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14. ABSTRACT

The overall objectives of this cooperative agreement are to conduct research in pursuit of identifying the physiologic mechanisms responsible for the symptoms of pain, fatigue, and memory difficulties commonly seen in patients with Chronic Multisymptom Illnesses (CMI) (i.e., fibromyalgia, chronic fatigue syndrome, Gulf War Illnesses, etc.); to identify the risk factors for developing these syndromes as well as programs aimed at both preventing these illnesses and treating established cases. These objectives will be achieved through multiple research studies using innovative, technologically advanced (e.g., functional MRI and telemedicine) methodologies in a multidisciplinary environment. Various studies will be conducted to explore all aspects of pain processing, the effects of exercise deprivation and sleep reduction on symptomatology, the ability of exercise and/or cognitive behavioral therapies to alter patients' locus of control for pain, the neurobiological mechanism(s) of acupuncture on analgesia, the presence of hypersensitivity to auditory stimuli, and the effectiveness of cognitive behavioral therapy delivered via telemedicine and the internet. These studies will be conducted on well-characterized cohorts of CMI subjects and healthy controls taken from our burgeoning subject registry. Research will occur over the next 3 years at the University of Michigan, Ann Arbor, MI and Avera Research Institute, Sioux Falls, SD.

15. SUBJECT TERMS
chronic multisymptom illnesses, fibromyalgia, Gulf War Illness, chronic pain

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Mechanisms in Chronic Multisymptom Illnesses
PI: Daniel J. Clauw, MD
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INTRODUCTION:

Researchers in the Chronic Pain and Fatigue Research Center (CPFRC) and collaborators within the University of Michigan and at Avera McKennan Research Hospital in Sioux Falls, SD are conducting research on human subjects in pursuit of the following overall objectives: to identify the physiologic mechanisms responsible for three prominent symptoms (pain, fatigue, and memory difficulties) of Chronic Multisymptom Illnesses (CMI) (i.e., fibromyalgia [FM], chronic fatigue syndrome [CFS], Gulf War Illnesses, etc.); and to identify the risk factors for developing these syndromes, as well as programs aimed at both prevention of these illnesses and treatment of established cases. These objectives will be achieved in a multidisciplinary environment with use of innovative, technologically advanced methodologies (e.g., using functional MRI [fMRI] and Positron Emission Tomography [PET], assessments of sensory processing, autonomic, and hypothalamic pituitary adrenal functions) and use of the internet and telemedicine to disseminate an educational intervention.

BODY:

The Specific Aims of this overarching research program are to continue to develop a registry of research subjects and healthy controls to be applied to ongoing recruitment efforts; to extensively study the cognitive, psychological and neurobiological measures of pain processing in this spectrum of illnesses; to determine whether an established non-pharmacological intervention (Cognitive Behavioral Therapy [CBT]) is effective when administered using an internet-based educational intervention; to explore both the physiologic and treatment effects of exercise and sleep on these illnesses; to study the neurobiological and psychological risks for developing these illnesses after an episode of trauma (in this case motor vehicle accident); to determine if individuals with FM suffer from an overall heightened sensitivity to physical stimuli (in this case auditory); to examine the effects of relaxation therapy and exercise training on pain locus of control, specifically to determine whether these interventions can alter patients' pain locus of control from an external to an internal drive; to study the neurobiological mechanism(s) of acupuncture analgesia from a Western perspective on patients with FM. These Aims are being addressed in eight individual research studies, each of which is described below with a brief overview of the study and a status update as of the writing of this report.

All interested participants who visit the CPFRC complete an extensive screening protocol, the Subject Registry, before participating in a specific study. Once screened, participants will then take part in the study or studies for which they qualify. A series of studies (titles in bold) will be performed at the University of Michigan and at Avera-McKennan Research Hospital as indicated below.

University of Michigan, Ann Arbor, MI:

1. Subject Registry for Interdisciplinary Studies of Chronic Multisymptom Illnesses at the University of Michigan

Study Overview: This protocol involves the development of a centralized subject registry that (a) recruits interested volunteers, (b) provides a general first-level screening of participants, and

(c) informs volunteers of current or future studies for which they might undergo a non-redundant and briefer study-specific screening. In addition to the demographic information gathered during initial phone contacts, the screening process generates a spectrum of information on each candidate regarding their general physical and psychiatric (Axis I and II) status, their specific CMI symptomatology, and the influence/interplay of CMI symptoms on their life. The subject registry also serves as a repository for genetic studies that will examine the genetic polymorphisms that are associated with a higher risk of developing these disorders.

Status/Results to date: For the calendar year of January 1, 2006 through this report, we have recruited 135 new subjects. This brings our total number of subjects for the Registry to 380. We have continued to schedule and screen individuals for enrollment in the CPFRC Subject Registry.

Although the inclusion/exclusion criteria for the Registry has remained stable, recruitment efforts have become more 'targeted'. Over the last year, we have provided prospective research candidates with more feedback regarding the likelihood of their being able to participate in specific hypothesis-based studies. This has minimized the disappointment and frustration previously voiced by candidates who successfully completed the screening process but were then unable to participate in specific studies.

Given that the majority of our studies include brain imaging, candidates are thus cautioned that being left-handed or claustrophobic, using opioid medications on a maintenance basis, and/or having a BMI above 36 may exclude them from participation in studies involving brain scans.

As mentioned above, the Registry is currently a repository for genetic information. In the near future, a new, hypothesis-driven protocol will be submitted to the DOD HSRRB to seek approval to complete genetic analyses using data from subjects who consented to have their DNA collected and stored.

2. The Effect of Exercise and Sleep Deprivation on the Development of CMI Symptoms

Study Overview: This study assesses the effects of sleep and exercise deprivation in healthy normal young adults. A previous DoD-funded study conducted by our group showed that some healthy individuals who were exercising regularly developed pain, fatigue, memory problems, and mood disturbances when they stopped performing exercise for one week, and that those that developed these symptoms had hypo- or hyperactivity of the autonomic and hypothalamic pituitary adrenal (HPA) axes at baseline (when they were exercising and were symptom-free) (1). This current study uses a 2 X 2 design to study the additive and synergistic effects of exercise or sleep deprivation (or both) on the development of these symptoms, as well as the autonomic and HPA predictors of developing these symptoms. Since exercise and sleep deprivation are both common sequelae in the battlefield and during deployment this study provides information of direct relevance to military preparedness, as well as information on how soldiers might be screened for the propensity to develop somatic symptoms during such conditions.

Status/Results to date: As of this report, a total of 93 individuals have enrolled in this protocol since we initiated recruitment in July of 2004. Of these, 59 were enrolled during the past 12 months. All subjects have been randomly assigned to one of four study arms: (1) Exercise deprivation with normal sleep, (2) Normal exercise with sleep deprivation, (3) Both exercise and sleep deprivation, or (4) Normal exercise and normal sleep.

Our preliminary analyses have thus far supported our first three hypotheses that either sleep or exercise deprivation will lend itself to somatic symptom presentation in otherwise healthy active individuals, with the combination of both sleep and exercise deprivation acting in concert to produce a greater effect on symptoms than seen with either intervention alone. Furthermore, we also have evidence supporting hypothesis #4, that baseline physiological parameters will predict which participants develop symptoms like those commonly seen in patients with chronic multi-symptom illnesses.

We translated these results into two abstracts, each of which will be presented at the upcoming national meeting for the American College of Rheumatology and are included, with detailed results, in the appendices. With respect to hypotheses #1-3, we first entered both deprivation conditions into a 2-way ANOVA with various symptom outcomes as the dependent variable. Among healthy individuals, a subset is prone to acute symptom development following disruption to their normal routine, with the general trend suggesting that a combined sleep/exercise restriction elicits the highest level of symptom increase, followed by sleep restriction alone, and lastly, by exercise restriction alone. [see Abstract #24]

For hypothesis #4 we calculated pearson product moment correlations to assess the association between two physiological parameters (baseline heart rate variability and baseline morning cortisol levels) and changes in symptoms (deprivation minus baseline). The data suggest that baseline physiological measures can predict subsequent increases in symptoms after sleep and exercise restriction. In aggregate, these results lend credence to our overarching hypothesis that low hypothalamic-pituitary adrenal axis and autonomic nervous system function represent a diathesis that predisposes individuals to development of somatic and cognitive symptoms after exposure to a stressor. [see Abstract #19]

3. Outcome of Patients Seen in the Emergency Department (ED) after Motor Vehicle Collision (MVC)

Study Overview: This study examines the neurobiological and psychological predictors of chronic symptoms such as regional or widespread pain, depression, or post-traumatic stress disorder (PTSD) following a stressful traumatic event: a motor vehicle accident. Just as with the above study, our pilot data suggest that the autonomic and HPA measures taken within the ED are predictive of the development of chronic pain or PTSD following such trauma. Individuals that are seen in the ED immediately following a motor vehicle accident that do not have a head injury, fracture or require hospitalization receive an extensive testing paradigm, including psychophysical testing and psychological assessments in the ED. These individuals are followed for 6 months and tested again with the same paradigm. Individuals in this study also undergo fMRI testing to examine predictor of chronic pain after a traumatic event. In addition to identifying physiological and psychological characteristics that predict the development of chronic pain or PTSD following this type of trauma, we have applied for DOD, NIH and CDC funding to perform a companion treatment trial examining whether a beta blocker (propanolol) will prevent the development of these chronic symptoms in a sub-group of high-risk individuals seen in the ED after MVC.

Status/Results to date: Recruitment for this study began in early 2006 and is currently ongoing. All participants who remain in the study will be assessed 3-7 days after MVC, again at 1 month following MVC, and finally, at 6 months following MVC. As of this report, 49 subjects have been enrolled in this project; 48 have reached one-month post-MVC follow up.

Preliminary findings indicate that among the initial 48 subjects enrolled in this study, persistent MVC-related neck and back pain symptoms were strongly associated with persistent PTSD. This suggests not only a frequent comorbidity of PTSD and chronic pain symptoms following MVC but also that pain reported immediately post-MVC is a strong risk factor for developing both disorders. [see Abstract #23]

In this same group of subjects, baseline somatic symptoms were predictive of both pain and psychological sequelae 1 month following MVC; however, baseline depression, anxiety and perceived stress were only predictive of psychological symptom development, not pain development, at 1 month following MVC. [see Abstract #29]

Pain beliefs and coping strategies that were initially assessed 3-7 days following MVC were predictive of the development of pain and psychological symptoms at 1-month following MVC. [see Abstract #31] In addition, physiologic characteristics (cortisol and high frequency heart rate variability levels) were associated with 1-month post-MVC pain and psychological sequelae. This information could help identify individuals who may be at risk for developing symptoms following a traumatic incident as well as giving insight into the pathophysiology of chronic pain disorders. [see Abstract #25] These findings will be presented at the upcoming annual conference for the American College of Rheumatology; complete abstracts with detailed results have been included in the appendices.

4. Mechanisms of Acupuncture Analgesia

Study Overview: In an innovative mix of modern technology and alternative therapies, we are using acupuncture as a potential placebo, and fMRI, PET, and magnetic resonance spectroscopy (SPECT) to determine specific neurological mechanisms of placebo analgesia. Within this study, we will better define opioidergic mechanisms that underlie pain and the placebo effect. Our preliminary data from this study suggest that patients with fibromyalgia have evidence of increased occupation of mu opioid receptors at baseline, suggesting that their endogenous opioidergic systems are maximally activated and in spite of this they are still experiencing severe pain. If these findings are confirmed it may help explain why opioid drugs are not clinically effective in chronic pain conditions such as fibromyalgia. Additional findings are listed below.

Status/Results to date: As of this report, 25 subjects have completed their participation in this study and 1 subject is currently in process. We anticipate recruiting an additional 25 subjects and will employ SPECT technology moving forward.

Three abstracts containing preliminary results have been accepted for presentation during the upcoming annual conference for the American College of Rheumatology. The complete abstracts with detailed results are included in the appendices. Major findings from each of the abstracts include: 1) Using fMRI technology in a longitudinal study pre- and post-acupuncture or sham treatment (9 treatments over 4 weeks), fibromyalgia subjects exhibited reduced sensitivity to evoked pressure pain as indicated by activations in the insula. [see Abstract #22] 2) To explore the role of mu-opiod receptor (MOR) availability in pain perception, fibromyalgia subjects underwent one acupuncture or one sham treatment intervention during a PET scanning session. Patients reported significantly reduced clinical pain simultaneous to imaging evidence of increased MOR availability in specific areas of their brain (nucleus accumbens and bilateral amygdala). These results implicate short-term modulation of this analgesic system in chronic pain reduction. [see Abstract #28] 3) With the use of PET technology, fibromyalgia subjects showed decreased MOR binding potential despite exhibiting augmented central pain processing revelaed with the use of fMRI technology. Not only does this reflect the value of using multiple

imaging techniques, it also suggests that augmented pain processing in fibromyalgia is not due to attenuated function of the intrinsic opioid system. [see Abstract #21] These preliminary findings regarding MOR will be further explored and developed.

5. Pain Mechanisms in Chronic Multisymptom Illnesses (CMI)

Study Overview: This study aims to assess sensory processing abnormalities in CMI. Methods include various psychophysical paradigms (ascending stimuli, random stimuli, pressure, temperature, etc.) and fMRI to extensively examine the activity of endogenous analgesic systems including descending antinociceptive activity (diffuse noxious inhibitory controls [DNIC]), aberrant afferent sensory stimuli processing, and abnormal cortical and sub-cortical central nervous system function in groups with various CMI. This study also examines the extent to which cognitive or psychological processes affect pain processing in both normal individuals and individuals with these illnesses. Finally, this study will explore whether individuals with chronic pain may have a global disturbance in sensory processing by concurrently measuring auditory threshold and pain thresholds.

Status/Results to date: As of this report, 93 subjects have been enrolled in this study. Thus far, subjects have undergone several variations of psychophysical testing and fMRI paradigms to explore pain mechanisms in CMI. In 2005-2006, ten abstracts have been developed from preliminary findings of these studies. Of these, five will be presented at the upcoming annual conference for the American College of Rheumatology. Major findings from these abstracts are described below; all abstracts with detailed results are included in the appendices.

Neuroimaging studies of pain focus on stimulus-evoked increases in activity and infrequently address "task induced deactivation" (TID). To explore TIDs, 25 fibromyalgia patients and 15 healthy controls experienced pressure pain testing while in the fMRI scanner. We observed TIDs in the primary somatosensory cortex that are likely representing reduced attention during painful stimulation. In the prefrontal cortex, we noted an association between stimulation "off" activity and preceding pain magnitude, which suggests a minor role of pain relief mechanisms in the prefrontal TIDs. We also observed an inverse relationship with pain magnitude and subsequent activity in pain processing regions that is consistent with either a fast acting suppression induced by painful stimulation or a sensory persistence evoked by less painful or innocuous sensations. [see Abstract #4]

This mechanistic study uses innovative methods to explore various aspects of pain experience in the periphery and subsequent processing in the brain. Using pressure stimuli to the thumbnail while patients underwent fMRI, we evaluated whether differences in overall sensitivity extended to non-painful, innocuous pressure stimuli. While both sensitive and insensitive fibromyalgia subjects experienced cerebral activation to innocuous pressure stimuli, the sensitive patients showed unique activations in primary somatosensory cortex, insula and middle frontal gyrus that were not observed in insensitive patients. Insensitive patients showed unique activations in bilateral temporal lobes and in ipsilateral middle frontal gyrus. The enhanced cerebral response to innocuous stimulation in the sensitive group suggests that previously observed augmentation of painful pressure may extend to pressures described as non-painful. [see Abstract #2]

Given that we frequently apply a painful pressure stimulus to the thumbnails of our fibromyalgia patients, we decided to explore whether the duration of that stimulus plays a role in patients' perception of pain or in their cerebral activations. Twenty fibromyalgia patients and 20 healthy controls experienced 5s of equally subjective painful thumb pressure presented at 25s

intervals or 25s of pressure presented at 50s intervals. In evaluating the complete 5s stimulus compared to the first 5 seconds of the 25s stimulus, healthy controls' response to 5s of stimulation was influenced by the subsequent duration of the stimulus. In contrast, fibromyalgia subjects showed a different pattern of cerebral response to the early part of the prolonged stimulus and no effects to the 5s stimulus. This temporal exploration lends further evidence of altered pain processing in fibromyalgia patients. [see Abstract #27]

In a second exploration of temporal sequences of evoked brain activity, fibromyalgia patients and healthy controls were exposed to one of the same stimulus patterns as described above: 5s of painful pressure presented at 25s intervals during fMRI. Temporal responses to the subsequent cerebral activations were classified as occurring early, middle, or late during the 5s stimuli. Healthy controls experienced immediate and late responses to stimuli that were not seen in the fibromyalgia patients (specific brain areas are outlined in the abstract). The cerebral activations in the fibromyalgia subjects were delayed and shortened, which is in contrast to the augmentation seen with longer (25-30s) pressure stimuli. This suggests that fibromyalgia patients experience a tonic inhibitory state with brief stimuli. [see Abstract #26]

Our group has done a significant amount of work evoking pain in fibromyalgia subjects and, often, comparing equally subjective pain in healthy controls. Given that fibromyalgia patients' pain network in the brain is activated at a lower objective stimulus intensity than healthy controls, we explored the fibromyalgia patient's resting state default network. We employed a technique called functional connectivity MRI (fcMRI), which uses low frequency BOLD oscillations to detect and explore the brain's natural default network. In a preliminary analysis of 10 fibromyalgia subjects and 10 healthy controls, fibromyalgia patients showed increased functional interconnections within the pain network during rest. This suggests that, in fibromyalgia patients, the pain network that is altered during painful stimulation is also altered during rest. [see Abstract #30]

Our group has begun a preliminary exploration into a widespread analgesic effect termed "diffuse noxious inhibitory controls" (DNIC), in particular, its effect on brainstem activity in fibromyalgia subjects. First, 10 healthy subjects received both a random (faint, moderate, slightly intense pain) to the left thumbnail and a DNIC stimulus of either a moderately intense painful pressure or an innocuous pressure to the right thumbnail during fMRI. Painful DNIC manipulation resulted in significant activation in ventral periaqueductal gray (vPAG) that was not seen in the no-DNIC stimulation or innocuous DNIC control stimulation conditions.[see Abstract #17] Further exploration of this mechanism in 11 fibromyalgia patients compared to these same 10 controls demonstrated activations in vPAG and related results that are consistent with defective DNIC in fibromyalgia. This defect also suggests dysfunction of the intrinsic descending vPAG-mediated system. [see Abstract #20]

Given that the cardinal symptom of fibromyalgia is pain, most of our work has explored pain mechanisms. However, many fibromyalgia patients report heightened sensitivity to other sensory stimuli as well. We examined auditory perceptions in fibromyalgia patients and healthy controls via standard hearing screening test, assessment of loudness discomfort levels (LDL), and hyperacusis questionnaire for subjective sensitivity to environmental sounds. These subjects also underwent pressure pain testing at the thumbnail. Similar to comparisons between fibromyalgia patients and healthy controls for pain perception, the noxious thresholds to both mechanical and auditory stimuli also display a left shift in stimulus response function for fibromyalgia patients. These data suggest that fibromyalgia may be a more global, sensory processing disorder than a specific pain disorder. [see Abstracts #12 & 14] Increased sensitivity

to sound, unusual intolerance to ordinary environmental sounds and ringing in the ears are common complaints of FM patients, even though they usually do not have any clinically and audiologically detectable ear disease. These data suggest that at least some FM patients have a generalized sensitivity to different sensory stimuli as a feature of disturbed global sensory processing, i.e., interoception. [see Abstract #15]

Finally, we explored the clinical relevance of evoked pain in a group of 38 subjects who presented with a diagnosis of fibromyalgia, chronic fatigue syndrome (CFS) or both. To determine which stimuli or stimulus intensities were most closely related to clinical pain, subjects experienced heat and pressure stimuli of varying subjective intensities and comparable levels of unpleasantness using random staircase methods. We also assessed clinical pain in these subjects using the McGill Pain Index and visual analog scales for both recalled and current pain. We found that pressure stimulation is the most relevant experimental pain model for reflecting clinical pain, perhaps due to fibromyalgia being characterized primarily by tenderness. [see Abstract #1]

6. Locus of Pain Control: Neural Substrates and Modifiability

Study Overview: Our preliminary study showed that individuals with an internal locus of pain control (i.e., they felt they could do something about their pain) had different neural processing of pain (based on fMRI), and less overall pain, than individuals with an external locus of pain control (who felt that they could not control their pain). In this study, we will evaluate the effectiveness of two non-pharmacological methods of improving pain locus of control in patients with FM: (a) training in relaxation and (b) training in aerobic fitness (exercise). A standard care group of FM patients and a group of healthy controls will round out the 4 study arms. We will use real-time symptom monitoring and extensive psychological assessment to characterize subjects, and again use fMRI to measure pain processing. We hypothesize that modifying an individual's cognitions or thoughts about their pain in this manner will lead to neurobiological differences in pain processing on fMRI from the patient's baseline assessment to their assessment after they have had the relaxation or exercise interventions.

Status/Results to date: This project has been approved by the DOD HSRRB. It is funded primarily by the NIH but will use supplemental funds from the DOD. DOD funds for this study will be used for fMRI scan once the NIH funds for fMRI have been exhausted. Recruitment for this study began in August 2005 and is currently ongoing. To date, 56 subjects have been recruited for this study. Subjects have been recruited into all 4 arms of the study in a random permuted blocks strategy that randomly assigns the first 5 FM subjects to one of the three arms, the next five FM subjects to one of the remaining two arms and the last 5 FM subjects to the remaining arm. Healthy controls are recruited into the final comparison arm. This randomization strategy permits the interventions to be conducted in a group format. Thus far, we are on schedule to complete 25 subjects in each arm. Abstracts/manuscripts will be developed as soon as sufficient data has been collected to provide meaningful results.

Partnership with Avera-McKennan Research Hospital, Sioux Falls, SD:

7. Internet and Telehealth Enhanced CBT for the Management of Fibromyalgia

Study Overview: This non-pharmacologic treatment intervention is designed to test the efficacy and efficiency of delivering CBT to persons with CMI using telemedicine and internet approaches. Further, this study will develop and test the efficacy of a multidisciplinary

educational CD given to chronic pain patients to improve pain and fatigue symptoms as well as function and overall quality of life. This project is being pursued with the Avera-McKennan Research Hospital. Given that as many as 14% of active duty personnel experience chronic symptom-based conditions and that this spectrum of illness occurred much more frequently after the Gulf War and other deployments, this project could have enormous impact on how these service members receive healthcare.

Status/Results to date: The website and CD development were recently completed and integrated with the electronic data capture system so that this entire study is online. Subject recruitment began in August 2006 and is currently ongoing. As of this report, 3 subjects have been enrolled.

The content of the multidisciplinary educational CD covers three main topic areas: overview of fibromyalgia including a discussion of causes and treatment advice; symptom management including medications and cognitive behavioral therapy skills such as exercise, sleep, relaxation, and pleasant activities; and lifestyle management such as goal setting, problem solving, pacing, reframing, and communication. The educational CD contains standardized video lectures, homework assignments to practice skills learned, and an interactive goal tracking feature. This CD is also available as a website, which contains a chat room accessible to study participants and a link to electronic self-report forms. Web access is restricted to study participants who have signed a consent form, obtained a study id, and created a password. Since this site is not accessible to the general public, several screen shots have been included in the appendices to give examples of content and appearance.

Abstracts/manuscripts will be developed as soon as sufficient data has been collected to provide meaningful results regarding this new approach to healthcare delivery for fibromyalgia patients as well as patients' satisfaction with their website/CD experiences.

Other Notable Findings and Activities:

In a general analysis of symptoms and comorbidities for fibromyalgia and Gulf War Illnesses (GWI), we focused our analysis on 49 patients who presented with fibromyalgia or GWI. We correlated their data from a symptom checklist containing 51 symptoms occurring over the last 3 months with measures of pain, fatigue, perceived function, and memory complaints. Physical complaints were not associated with fatigue but they predicted variance in perceived function, verbal memory, and visual-spatial memory. This suggests that the number of physical complaints observed in these disorders are significantly associated with pain and are uniquely related to physical function and memory complaints independent of pain intensity. [see Abstract #13]

Given previous findings from our group that have identified neurobiological differences in female fibromyalgia patients with and without self-reported history of childhood physical or sexual abuse, we decided to explore the pain processing mechanisms of these patients via fMRI with a painful pressure stimulation. Women with a self-reported history of physical or sexual abuse experienced significantly increased activations in several areas of the brain suggesting that this history is associated with variations in pain processing in fibromyalgia. [see Abstract #3]

In May 2006, the CPFRC co-hosted a research symposium in conjunction with the faculty of the Division of Rheumatology and the Rheumatic Diseases Core Center at the University of Michigan, entitled "Chronic Pain Treatment: Barriers to Care vs. Evidence of Success." UM and invited practitioners and researchers from diverse backgrounds shared their

ideas on chronic pain treatment. By addressing the important role in which chronic pain treatment impacts the community – patients, clinicians, researchers, managed care providers, industry, and health systems – the interactions and exchanges of knowledge and ideas held at this symposium were aimed at leading to improved treatment and care for patients with chronic pain. The objectives were to provide physicians, researchers, and healthcare professionals with better understanding and skills to:

- identify how differences in the setting of pain care influence therapy.
- identify the risk factors for individuals transitioning from acute to chronic pain.
- identify the mechanistic subsets of individuals with chronic pain.
- identify new models of care for pain patients that might improve quality and cost of care.

This symposium was intended to serve as a catalyst for change and as a means to provide further motivation to seek and develop new and improved methods for chronic pain treatment.

Finally, over the past year members of our research team have participated in campus and community-wide outreach efforts including speaking to the UM medical research community regarding clinical research coordinating and adverse event reporting; communicating latest research findings and research opportunities to support group leaders; providing education and opportunities for research participation to interested patrons of community-based health fairs; presenting abstracts at the UM Internal Medicine Research Day; and maintaining educational websites that focus on Gulf War Illness and chronic multisymptom illnesses including a list of the Center's publications and other reputable websites, and a description of who we are and what research opportunities exist within the Center.

KEY RESEARCH ACCOMPLISHMENTS:

- Both the exercise/sleep deprivation study (study #2 above) and post-MVC study (study #3 above) are demonstrating that **baseline** abnormalities in autonomic and hypothalamic pituitary adrenal function predict the subsequent development of somatic symptoms. If this finding is confirmed it would represent a major paradigm shift in how these illnesses are viewed because, previously, we thought these abnormalities were causing the illness. This would also make it possible for the DOD to screen recruits for autonomic and HPA function and identify those who might be at risk of various sequelae following exposure to stress.
- In aggregate our functional imaging studies continue to show a number of objective abnormalities in pain processing in individuals with chronic multisymptom illnesses. Perhaps the most remarkable finding is that it appears as though the endogenous opioid system is already maximally activated in patients with fibromyalgia because at baseline the mu opioid receptor binding is diminished, and this value correlates strongly with clinical pain ratings.
- The treatment study underway looking at electronic media to help manage fibromyalgia represents the "cutting edge" of the pain field and could be useful in a number of clinical settings if shown to be effective.

REPORTABLE OUTCOMES:

The following list of journal articles, published book chapters, manuscripts submitted for review and abstracts presented during the period of this report or accepted for presentation during upcoming scientific conferences fully describes the reportable outcomes that have resulted from this research:

Journal Articles – 2005 (pdfs of each are appended unless otherwise noted by *)

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Links to Websites:

http://www.med.umich.edu/painresearch/ - Specific to the CPFRC

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CONCLUSION:

Both the exercise/sleep deprivation study (study #2 above) and post-MVC study (study #3 above) are demonstrating that **baseline** abnormalities in autonomic and hypothalamic pituitary adrenal function predict the subsequent development of somatic symptoms. If this finding is confirmed it would represent a major paradigm shift in how these illnesses are viewed, because previously we thought these abnormalities were causing the illness. This would also make it possible for the DoD to screen recruits for autonomic and HPA function and identify those who might be at risk of various sequelae following exposure to stress.

In aggregate our functional imaging studies continue to show a number of objective abnormalities in pain processing in individuals with chronic multisymptom illnesses. Perhaps the most remarkable finding is that it appears as though the endogenous opioid system is already maximally activated in patients with fibromyalgia, because at baseline the mu opioid receptor biding is diminished, and this value correlates strongly with clinical pain ratings.

The treatment study underway looking at electronic media to help manage fibromyalgia represents the "cutting edge" of the pain field, and could be useful in a number of clinical settings if shown to be effective.

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APPENDICES:

The attached appendices contain information that supplements, clarifies or supports the text, including original copies of journal articles and abstracts listed in the Reportable Outcomes section above as well as website screen shots as described in study #7 above.

APPENDICES

Journal Articles – 2005

Journal Articles – 2005

Abstracts – 2005

Abstracts – 2006

“Living Well with Fibromyalgia”
Website Screen Shots

Journal Articles – 2005

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Human neuroglobin protein in cerebrospinal fluid

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Abstract

Background: Neuroglobin is a hexacoordinated member of the globin family of proteins. It is predominantly localized to various brain regions and retina where it may play a role in protection against ischemia and nitric oxide-induced neural injury. Cerebrospinal fluid was collected from 12 chronic regional or systemic pain and 5 control subjects. Proteins were precipitated by addition of 50% 0.2 N acetic acid, 50% ethanol, 0.02% sodium bisulfite. The pellet was extensively digested with trypsin. Peptides were separated by capillary liquid chromatography using a gradient from 95% water to 95% acetonitrile in 0.2% formic acid, and eluted through a nanoelectrospray ionization interface into a quadrapole – time-of-flight dual mass spectrometer (QToF2, Waters, Milford, MA). Peptides were sequenced (PepSeq, MassLynx v3.5) and proteins identified using MASCOT ®.

Results: Six different neuroglobin peptides were identified in various combinations in 3 of 9 female pain subjects, but none in male pain, or female or male control subjects.

Conclusion: This is the first description of neuroglobin in cerebrospinal fluid. The mechanism(s) leading to its release in chronic pain states remain to be defined.

Background

The protein constituents (proteome) of cerebrospinal fluid (CSF) are altered in disease states such as meningitis, but may also be more subtly altered in many other neural conditions. CSF has been difficult to investigate because of the need for invasive lumbar punctures and the small volumes of CSF available for analysis. This situation is now rapidly changing as methods requiring microliter volumes and sophisticated analysis tools such as proteomics become available [1,2]. Proteomics has made it possible to identify scores of proteins that have not been previously discovered in this fluid.

One such protein is neuroglobin. Neuroglobin is a recently identified member of the globin family. It binds oxygen with an affinity between that of myoglobin and hemoglobin [3,4]. Neuroglobin is 151 amino-acids long with a molecular mass of ≈ 17 kDa. The mouse and human genes are 94% identical. Neuroglobin is an ancient protein (estimated < 550 Myr old) that is more related to the annelid *Aphrodite aculeate* intracellular

Table 1: Amino acid sequence of neuroglobin peptides identified from human CSF using CapLC nanoESI Q-TOF tandem mass spectrometry.

#[a]	Amino Acids	M/z [b]	Z[c]	Molecular Weight		Δ[d]	Amino Acid Sequences	Time[e] (min)
				Calc.	Exp.			
1	1–10	423.98	3	1268.65	1268.91	0.25	(-)MERPEPELIR(Q)	37.02
1	15–30	580.73	3	1738.95	1739.18	0.23	(R)AVSRSPLEHGTVLFAR(L)	42.94
1	19–30	442.99	3	1325.71	1325.95	0.25	(R)SPLEHGTVLFAR(L)	42.68
1	131–146	580.04	3	1736.87	1737.10	0.24	(R)AAWSQLYGAVVQAMSR(G)	68.23
1	131–151	761.42	3	2281.06	2281.23	0.17	(R)AAWSQLYGAVVQAMSRGWDGE(-)	74.49
2	131–146	580.02	3	1736.87	1737.03	0.16	(R)AAWSQLYGAVVQAMSR(G)	68.24
2	131–151	761.37	3	2281.06	2281.09	0.03	(R)AAWSQLYGAVVQAMSRGWDGE(-)	74.54
3	1–10	423.97 [f]	3	1268.65	1268.88	0.23	(-)MERPEPELIR(Q)	37.31
3	15–30	435.82 [f]	4	1738.95	1739.27	0.32	(R)AVSRSPLEHGTVLFAR(L)	43.27
3	19–30	442.99	3	1325.71	1325.96	0.25	(R)SPLEHGTVLFAR(L)	43.01

a. Subject Number
b. Mass / charge ratio
c. Charge
d. Difference (error) between the experimental (Exp.) and calculated (Calc.) molecular weights
e. Elution time expressed in minutes.
f. Peptides in Subject 3 identified only with ProteinLynx Global Server using the SwissProt database.

globin (30% identify) [5] than to vertebrate myoglobin (<21% identity) and hemoglobin (<25% identity) [3]. Human neuroglobin mRNA is predominantly expressed in brain with high signal in the frontal lobe, subthalamic nucleus and thalamus. The concentration is estimated to be less of 0.01% of the total brain protein content [3]. Neuroglobin protein has not been previously detected in cerebrospinal fluids.

Results

Neuroglobin Peptides

Five peptides derived from neuroglobin (NCBInr ID accession 10864065) were identified using both the MASCOT software with NCBInr database and ProteinLynx Global Server with SwissProt database (Table 1). Two precursor ions with mass/charge (M/Z) ratios of 423.97 and 435.82 were identified in CSF sample #3 with the SwissProt, but not NCBInr, searches. Table 1 shows the mass-over-charge (m/z), charge state, elution time, position, sequence, molecular weight (M_r) for each peptide. The numbers of matching peptides were 5 in sample #1, 2 in sample #2, and 3 in sample #3. The peptides mapped 31.1%, 13.9% and 17.2%, respectively, of the total neuroglobin protein sequence. They matched amino acids 1–10 and 15–30 of the N-terminal and 131–151 of the C-terminal. Trypsin digestion missed cleavage sites at amino acids 18 and 146. Reproducibility was demonstrated by the consistent retention times for the same peptides from different subjects. No low abundance neuroglobin peptides were found in other samples. BLAST sequence analysis of all six peptides identified only one protein: hypothetical 16.9 kDa protein (neuroglobin: NREF and iProClass NF00135839; SwissProt/TrEMBL Q9NPG2).

Mass Spectrometry

Figures 1 through 5 show the tandem MS data for the 5 [M+H$^+$] precursor ions. The mass of each b- and y-fragment is listed. The amino acid sequence is shown at the top of each spectrum using the Roepstorff nomenclature [11]. The amino acid sequences were determined from both the N- and C-terminal directions. Figures 1 and 4 show two spectra from subject #1. Figures 3 and 5 show two spectra from subject #2. Figure 2 shows one spectrum from subject #3. Neuroglobin peptides were detected in 2 of the 3 CapLC runs for subjects #1 and #2, but only in 1 run for subject #3.

The peptides with M/z of 580 and 761 (Table 1) overlapped with the 761 ion having a missed tryptic cleavage point at Arg^{146}. Additional peptides were not identified, perhaps because we did not reduce disulfide bridges to reveal additional trypsin digestion sites. However, all the identified peptides were specific for neuroglobin, and so were appropriate markers for fast identification of this protein.

Neuroglobin and Pain Subjects

Neuroglobin-derived peptides were found in 3 of 9 female pain subjects, but none of the 3 male pain subjects; it was not detected in the 3 female or 2 male control subjects. Within the chronic pain group there was no association between the presence of neuroglobin and clinical factors such as age, extent or duration of pain, or tenderness to

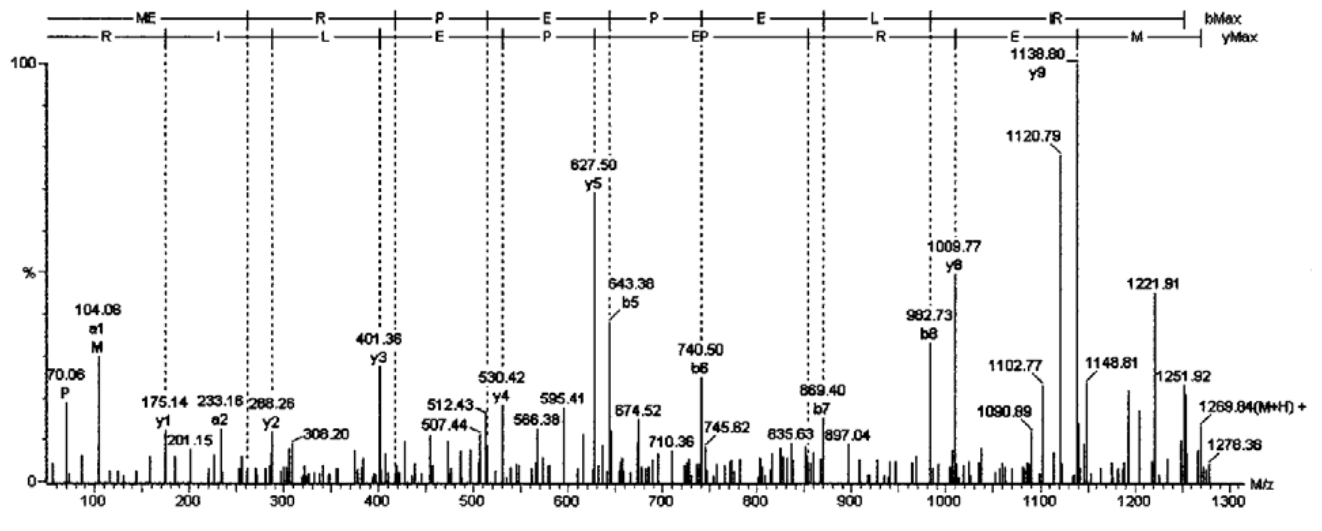

Figure 1
The tandem mass spectrum is shown for the neuroglobin amino acid 1 to 10 peptide. In this and the following figures, the top line represents the b-series, and the 2nd line the y-series. The x-axis presents M/z and the y-axis signal intensity. The numbers are the M/z values for each daughter ion (vertical lines).

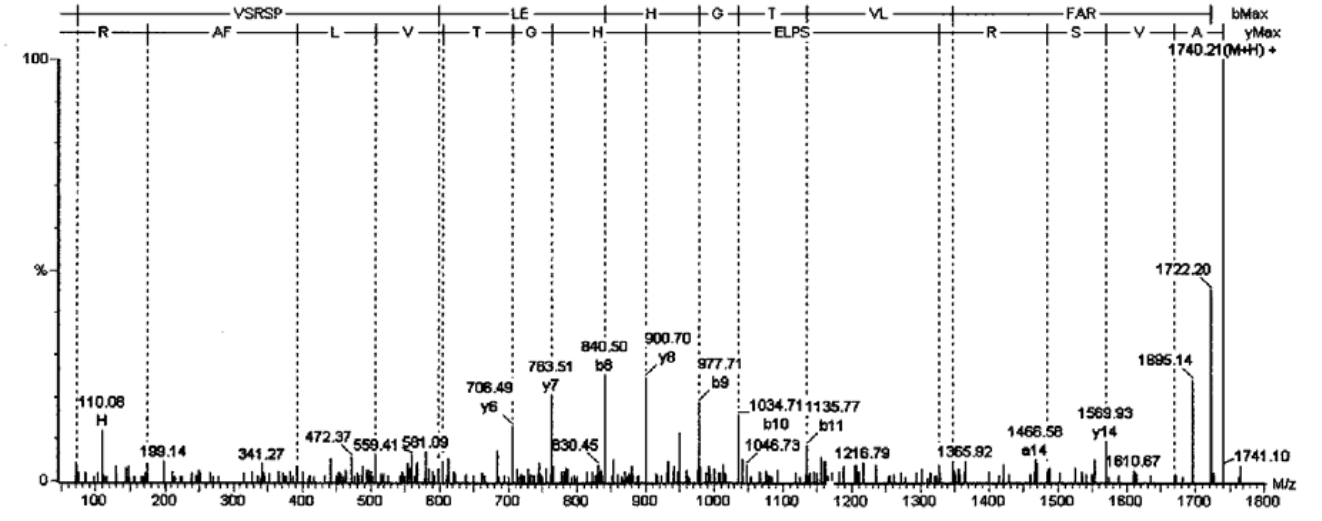

Figure 2
The tandem mass spectrum is shown for the neuroglobin amino acid 15 to 30 peptide.

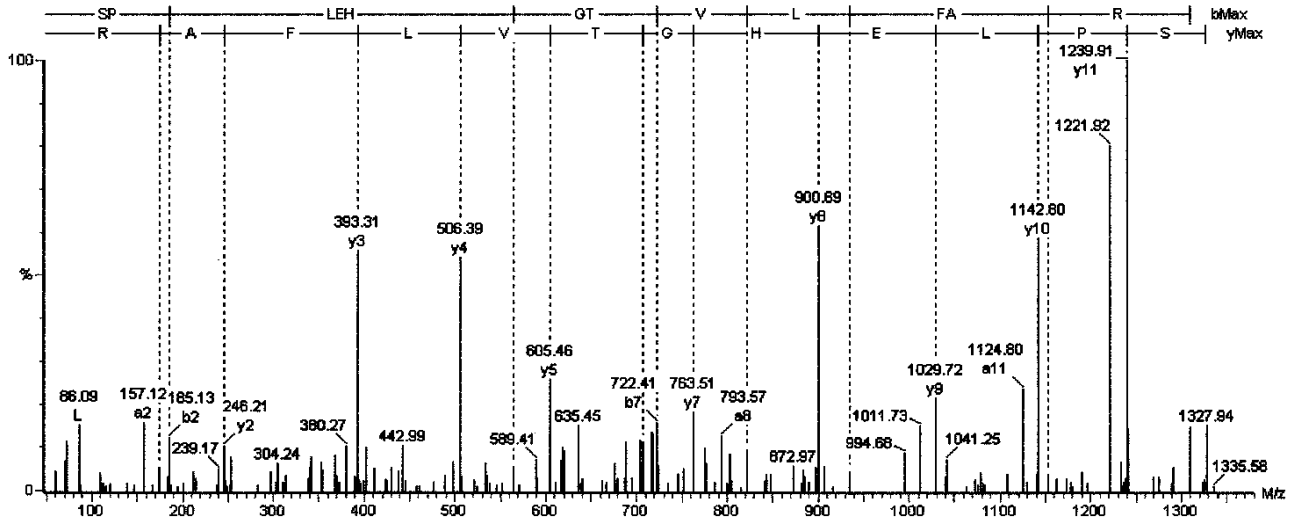

Figure 3
The tandem mass spectrum is shown for the neuroglobin amino acid 19 to 30 peptide.

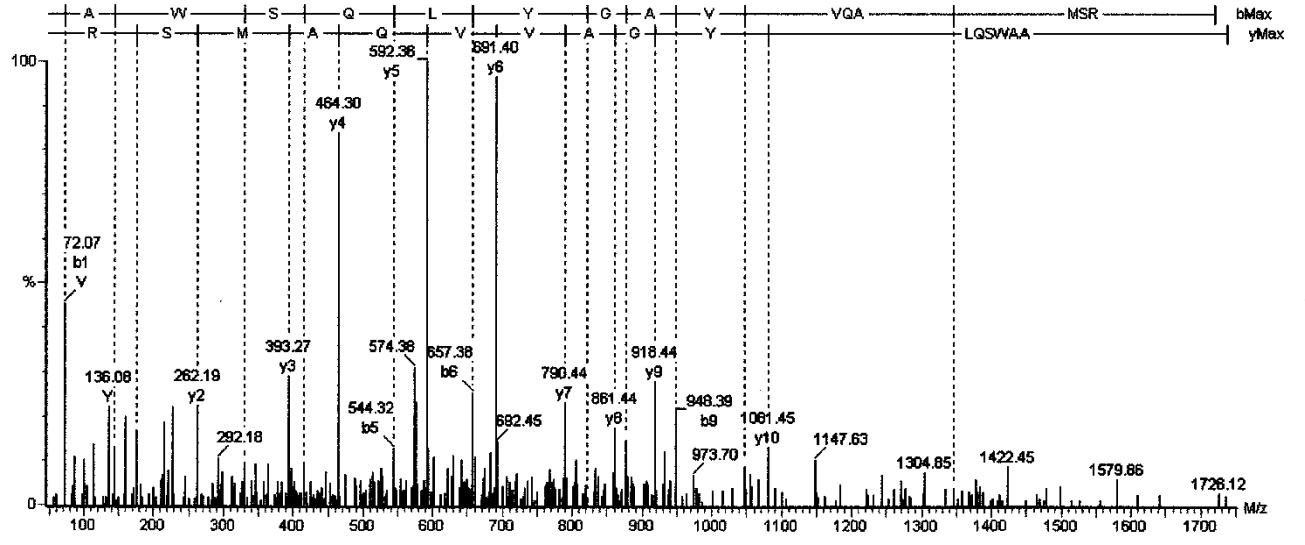

Figure 4
The tandem mass spectrum is shown for the neuroglobin amino acid 131 to 146 peptide.

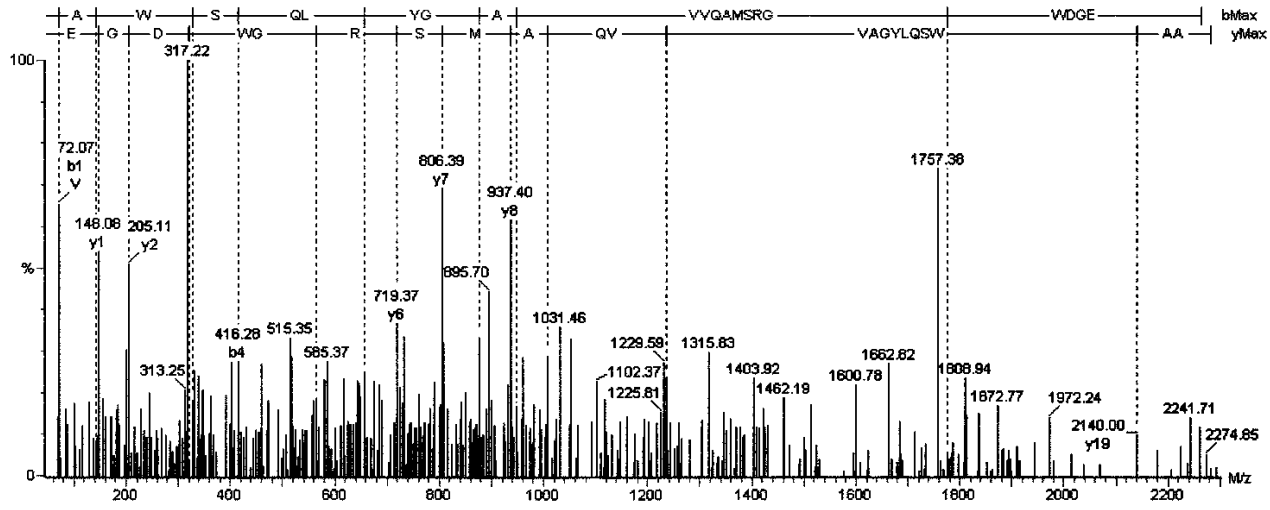

Figure 5
The tandem mass spectrum is shown for the neuroglobin amino acid 131 to 151 peptide.

pressure. No hemoglobin or cytoglobin [12,13] were detected.

Discussion

This is the first description of neuroglobin protein in the CSF of any species. Neuroglobin joins cytoglobin (histoglobin) in a new globin subfamily that forms hexacoordinated heme iron complexes [12,13]. These are distinct from the pentacoordinated hemoglobin and myoglobin.

The source of neuroglobin in the CSF is likely to be brain regions such as the subthalamic nuclei (60% of total brain neuroglobin mRNA expression), frontal lobe, thalamus, occipital pole, pituitary gland, and medulla oblongata [3,14]. Immunohistochemistry confirmed this distribution with strong staining in the hippocampus, thalamus, hypothalamus (especially the paraventricular nucleus) and brainstem nuclei of cranial nerves [15]. Expression was often patchy within these regions indicating that only select neurons expressed neuroglobin. Regions with high sensitivity to hypoxia such as the cerebral cortex had constitutive expression [15]. Spinal cord was a less likely source since its neuroglobin mRNA expression was less than 10% of that from the subthalamic nuclei. Neuroglobin mRNA was expressed in the retina [16] and in peripheral nerves suggesting that the mRNA was axonally transported and translated to distal neurons [17]. The protein has a cytoplasmic distribution [18]. Neuroglobin could provide oxygen for high energy consuming processes such as synaptic activity, neural plasticity, or efferent transmitter release as in nociceptive nerve axon responses.

Neuroglobin mRNA was also present in adrenal cells and the β cells of the pancreatic islets of Langerhans [14]. Roles in diabetes or hypoxia-induced insulin secretion are unstudied. These studies of mRNA expression should not be extrapolated into relative levels of protein expression or neuroglobin turnover since concordance between microarray and proteomic studies can be as low at 13% [19].

Neuroglobin is likely to serve as an intracellular oxygen depot to facilitate oxygen diffusion to the mitochondria. A role in oxygen supply was supported by the very high expression of neuroglobin mRNA in retinal neurons but not the supporting ocular epithelium and other structures [16]. Retinal neuroglobin concentrations were estimated at > 100 μM, compared to > 1 μM for the whole brain. The retinal and muscle oxygen tensions, oxygen affinities and tissue concentrations of neuroglobin and myoglobin were comparable suggesting that the two play homologous roles in their respective tissues.

Neuroglobin might act in certain circumstances to limit neural cellular damage during hypoxia. Neuroglobin expression was inversely correlated to the sensitivity of the

brain regions to ischemia [3]. For example, neuroglobin expression was 4 times higher in the cerebral cortex than the hippocampus, corresponding to the time for ischemia to cause half-maximal damage (19.1 and 12.7 min, respectively) in these tissues [20]. Neuroglobin-immunoreactive material was upregulated in the cytoplasm of neurons that were destined to survive acute cerebral ischemia, and was reduced in apoptotic neurons [21]. Hypoxic induction of neuroglobin was blocked by the mitogen-activated protein kinase/extracellular signal-regulated kinase kinase inhibitor PD98059 [22]. Like hemoglobin and myoglobin, hemin increased neuroglobin 4-fold through a separate signalling process mediated by protein kinase G and soluble guanylate cyclase. Hypoxia-inducible neuroprotective factor (HIF-1) that can induce β-globin production may play a role in neuroglobin induction. It is not clear if there are differential responses to intermittent, recurrent, or chronic cerebral ischemia.

Neuroglobin was also colocalized with nitric oxide synthase in the lateral tegmental nuclei, stria terminalis, habencule, nucleus of the tractus solitarius, periaqueductal grey matter, amygdala and subfornic organ [23]. The protein may act as a nitric oxide scavenger, a role that has also recently been proposed for myoglobin [24]. This function would protect against nitric oxide – induced damage that is part of hypoxia – ischemia related neuron injury. Nitric oxide appears to bind to the hexacoordinated deoxy ferrous form (F8His-Fe^{2+}-E7His) and displace the protein from the globin [25]. This affinity may be a double-edged sword, since neuroglobin, hemoglobin and myoglobin may protect *Plasmodium* and *Trypanosoma* from the antiparasitic effects of nitric oxide [26]. Neuroglobin may also play a protective role in carbon monoxide poisoning [27].

In this study, neuroglobin was qualitatively identified in CSF from 3 female subjects with chronic pain conditions. Females have greater pain sensitivity to pressure and other stimuli (lower pain thresholds) [28], but pain is not thought to induce neural hypoxia or any of the known triggers of neuroglobin expression [21].

It is tempting to speculate that the source of neuroglobin in our samples was from nuclei involved in pain transmission or regulation such as the thalamus, prefrontal cortex, amygdala, or spinal cord dorsal horn somatic pain synaptic regions (e.g. layers 1 and 2 of Rexed). The fact that neuroglobin was not detected in any of the control females in our study makes it unlikely that the expression was related to gender. Examination of additional normal and chronic pain subjects is underway to determine the factors that may be responsible for neuroglobin expression. It is also possible that the proteomic detection of neuroglobin varies depending upon sample preparation, signal-to-noise ratio for relatively low abundance proteins compared to albumin and immunoglobulins that are present in high abundance, duration of storage, factors related to trypsin digestion, capillary liquid chromatography, mass spectrometry or bioinformatic neuroglobin peptide detection. These technical factors are unlikely to be significant since our samples were treated identically and were stored for approximately equal amounts of time.

In contrast to neuroglobin's localization, cytoglobin-immunoreactive material was localized to the cellular nucleus in all tissues examined [14]. Mammalian cytoglobin genes display an unique exon-intron pattern with an additional exon resulting in a C-terminal extension of the protein that is not present in lower species such as zebra fish [29,30]. Again, it is not clear if cytoglobin acts as an oxygen depot or sink, free radical scavenger, oxygen-sensor or transcription factor. No evidence for cytoglobin was found in cerebrospinal fluid suggesting that nuclear degeneration was not present in any of our subjects.

Conclusion

This is the first description of neuroglobin in cerebrospinal fluid and in humans. Neuroglobin was identified in 3 of 9 female pain subjects. The role(s) for this ancient oxygen and nitric oxide binding protein in humans, and potential links to pain, remain to be fully determined.

Methods

After obtaining informed consent, lumbar punctures were performed on 17 subjects as part of an evaluation of pain mechanisms. Twelve patients had musculoskeletal pain and five were healthy control subjects. Cerebrospinal fluid samples were aliquoted and frozen at -70°C. Lipids and peptides were extracted from 200 μl of thawed CSF by adding an equal volume of 50% ethanol, 50% 0.2 N acetic acid 0.02% sodium bisulfite ("acid-ethanol") [6]. Centrifuged pellets were reconstituted in 50 μl of 0.1 M ammonium bicarbonate buffer (pH 7.8) and digested with trypsin (protein-enzyme ratios of 20:1) at 37°C overnight. Digested peptides were separated by capillary liquid chromatography (CapLC, Waters, Milford, MA) over a Zorbax 18WSB reverse phase column (100 mm × 0.15 mm inner diameter) (Micro-Tech Scientific, Sunnyvale, CA) at room temperature for 100 min using a gradient starting at 95% solvent A (aqueous solution of 0.2% formic acid) and ending with 95% solvent B (acetonitrile with 0.2% formic acid). The elution was performed at a flow-rate of 1 μl/min.

The column eluate was pumped through a nanoelectrospray interface into a quadrapole – time of flight (Q-TOF-2, Waters, Milford, MA) mass spectrometer. MASSLYNX version 3.5 software was used to control the CapLC and Q-ToF-2, data acquisition, processing, and determination

of peptide sequences. The protein identification was performed with the MASCOT MS/MS ion search software http://www.matrixscience.com and NCBInr protein database [7,8], and with ProteinLynx Global Server Web (Waters) with SwissProt database. The BLAST algorithm was used to compare protein queries to database sequences (e.g. Protein Information Resource, PIR, http://www.pir.georgetown.edu) [9,10], proteins derived from GenBank coding sequences, and PDB atomic coordinates.

Samples were assessed by CapLC-Q-ToF-2 in triplicate. At least 2 separate peptides from neuroglobin had to identify in each individual sample to ensure that this protein, and not a related protein, was present. In an attempt to detect low abundance expression of neuroglobin peptide ions that were not selected by MS-MS (false negative results), all MS data from the appropriate CapLC retention times were reassessed at high resolution. Positive results (MS data) were checked to see if ions in MS were present but not in MS-MS for other pieces. All putative neuroglobin peptide spectra were sequenced using PepSeq (Waters) and confirmed by visual inspection.

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

Casado B [1,4], Sample preparation, chromatography, mass spectrometry and manuscript preparation

Pannell LK [2], Supervision and assistance with chromatography and mass spectrometry and manuscript preparation

Whalen G [1], Sample preparation

Clauw DJ [3], Clinical investigation of subjects

Baraniuk JN [1,*], Organization of study and selection of samples, preparation of manuscript

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Efficacy of Milnacipran in Patients with Fibromyalgia

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ABSTRACT. ***Objective.*** Fibromyalgia (FM) is a common musculoskeletal condition characterized by widespread pain, tenderness, and a variety of other somatic symptoms. Current treatments are modestly effective. Arguably, the best studied and most effective compounds are tricyclic antidepressants (TCA). Milnacipran, a nontricyclic compound that inhibits the reuptake of both serotonin and norepinephrine, may provide many of the beneficial effects of TCA with a superior side effect profile.

Methods. One hundred twenty-five patients with FM were randomly assigned in a 3:3:2 ratio to receive milnacipran twice daily, milnacipran once daily, or placebo for 3 months in a double-blind dose-escalation trial; 92% of twice-daily and 81% of once-daily participants achieved dose escalation to the target milnacipran dose of 200 mg.

Results. The primary endpoint was reduction of pain. Both the once- and twice-daily groups showed statistically significant improvements in pain, as well as improvements in global well being, fatigue, and other domains. Response rates for patients receiving milnacipran were equal in patients with and without comorbid depression, but placebo response rates were considerably higher in depressed patients, leading to significantly greater overall efficacy in the nondepressed group.

Conclusion. In this Phase II study, milnacipran led to statistically significant improvements in pain and other symptoms of FM. The effect sizes were equal to those previously found with TCA, and the drug was generally well tolerated. (J Rheumatol 2005;32:1975–85)

Key Indexing Terms:
FIBROMYALGIA PAIN MILNACIPRAN ANTIDEPRESSANT ANALGESIC

Fibromyalgia (FM), also known as fibromyalgia syndrome, is a common systemic disorder estimated to affect 2% to 4% of the population, second in prevalence in rheumatologic practice to osteoarthritis[1,2]. While considerable disagreement exists regarding its etiology and diagnosis, there is increasing evidence and acceptance that FM is indeed a medical problem reflecting a generalized heightened perception of sensory stimuli leading to a condition of chronic, widespread pain[3,4]. There has also been a parallel recognition that common somatic syndromes such as irritable bowel syndrome, tension and migraine headache, and temporomandibular syndrome share overlapping symptom expression and underlying mechanisms with FM[5-8].

In 1990, the American College of Rheumatology (ACR) established classification criteria that have standardized research of FM[1]. These criteria require that an individual have both chronic widespread pain involving the axial skeleton and all 4 quadrants of the body as well as the presence of 11 of 18 tender points on examination[1]. Although pain and tenderness are the defining features of this illness, individuals who fulfill these criteria commonly suffer a variety of other symptoms including fatigue, sleep disturbances, migraine or tension headaches, irritable bowel symptoms, and changes in urinary frequency. Although there is controversy about the terms used to describe this constellation of symptoms and whether these are "real diseases," they are extremely common and in many cases are refractory to presently available treatments[3].

A broad array of medications has been used to treat FM, including antidepressants, anticonvulsants, antispasticity agents, anxiolytics, sedatives, and opioids, with varying degrees of success[9]. Nonsteroidal antiinflammatory drugs (NSAID) and acetaminophen have also commonly been used, although there is little evidence of peripheral damage or inflammation in FM[10,11]. Unfortunately, while there are many potential medication options, few pragmatic clinical trials have been performed to inform clinician and patient decision-making. That there are no drugs currently approved

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by the US Food and Drug Administration for use in FM emphasizes the urgent need for more clinical trials of promising medications.

Of all medication options in FM, tricyclic antidepressants (TCA) have the most evidence for treatment efficacy, and are the cornerstone of most treatment paradigms[12]. These medications block the reuptake of both serotonin and norepinephrine[13], and are believed to decrease pain by modulating pain processing in the spinal cord[14]. Because TCA have many potential side effects, selective serotonin reuptake inhibitors (e.g. fluoxetine) have been tried in FM, but have not been found to be effective pain medications[15,16]. This has led to the belief that the blockade of both serotonin and norepinephrine (dual reuptake inhibition) is needed for efficiacy in pain reduction, a belief supported by the positive results of phase II studies of duloxetine in FM[17].

Milnacipran is a well characterized small molecule that, in a manner similar to duloxetine, functions as a selective reuptake inhibitor of both serotonin and noradrenaline[18]. However, milnacipran is unique in its preference toward norepinephrine reuptake inhibition, and also binds to NMDA receptors[18]. Unlike the TCA, milnacipran does not interact with histaminergic or muscarinic receptors or sodium channels, and thus lacks many side effects of TCA[19]. The safety of milnacipran has been established in clinical trials and in its use as an approved antidepressant in 30 countries. However, no randomized clinical trials have evaluated the analgesic properties of milnacipran.

We evaluated the overall analgesic efficacy and safety of milnacipran in a sample of patients with FM. The primary endpoint was improvement in pain. Secondary objectives included assessment of the influence of dosing strategy (BID versus QD) and the effect of milnacipran on other symptoms of FM including fatigue, mood, physical function, and sleep disturbances.

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MATERIALS AND METHODS

Participants. Fourteen sites with extensive FM experience participated in the trial. The outpatient protocol for 12 sites was approved by a central institutional review board (Western Institutional Review Board). The remaining 2 centers were approved by local boards.

The screening assessment included a medical and psychological history, physical and laboratory examinations, and the Mini International Neuropsychiatric Interview (MINI)[21]. Patients were eligible for the study if they were aged between 18 and 70 years, met the ACR 1990 research criteria for FM, and reported a pain score ≥ 10 on a 20-point logarithmic pain scale (Gracely scale) at the time of the baseline assessment. In addition, patients had to be willing to use a contraceptive (if female) and to withdraw from all central nervous system-active therapies. Exclusion criteria included psychosis; active suicidality; alcohol or substance abuse; concurrent autoimmune, inflammatory, infectious, or malignant disorder; known sleep apnea or prostatic hypertrophy; and abnormal baseline liver or kidney function tests. After giving informed consent, patients taking antidepressants, antiepileptics, centrally-acting muscle relaxants, hypnotics, and opioids and their derivatives were required to discontinue their medications over a period of one to 4 weeks. Stable doses of NSAID, aspirin, and acetaminophen were allowed during the study.

Study design and procedures. The study was a 3-month, randomized, double-blind comparison of milnacipran to placebo. Patients were allowed to escalate up to 200 mg milnacipran daily, or to their maximum tolerated dose. In addition, patients were randomized to receive their study drug either in one daily dose (QD) or 2 divided doses (BID). As summarized in Figure 1, the study design involved 4 phases: screening and washout, baseline assessment, dose escalation, and stable-dose phase. This was a short term, acute discontinuation trial; subjects were not followed after the trial concluded, and the data presented cannot be extrapolated to longterm effects.

For most patients, the screening and washout phase (if necessary) lasted for 2 weeks prior to randomization into a study group. Patients who were taking fluoxetine upon enrollment completed a washout phase of 4 weeks before being randomized into a study group. Per study guidelines, data collection began at the start of the baseline phase, after study subjects completed the washout phase. During the 2-week baseline phase, patients recorded their level of pain on electronic diaries (e-diaries). During the dose escalation phase, patients began taking study medication after being randomized to one of three arms. Weekly dose increased if the patient did not experience dose limiting side effects. If side effects developed, dose was reduced to that which was tolerated previously. The stable-dose phase was an 8-week period during which patients took medications at the final dose achieved (either 200 mg or the maximum tolerated dose).

After 2 weeks of baseline assessments, patients entered the third phase. Randomized assignment allocated each patient to one of 3 study arms: placebo, single daily dosing of milnacipran (QD), or twice daily divided dosing of milnacipran (BID). Randomization was performed by an independent contract research organization that generated randomization assignments and packaged drug in a block size of 8, in a ratio of 3:3:2 for QD:BID:placebo. An automated telephone response system operated by the same firm performed the patient treatment assignments using the previously generated randomization table. QD patients received milnacipran as a single dose taken with the morning meal and a placebo with the evening meal. BID patients received milnacipran as a divided dose with the morning and evening meals. Placebo-treated patients received morning and evening placebo capsules. All capsules were visually identical, and patients and investigators remained blinded to patients' treatment allocation. At the beginning of the escalation phase, all patients were instructed to take capsules with morning and evening meals for the first week, after which they should telephone the study center to report dose-limiting side effects (see Figure 1). At each telephone call, the center advised them to maintain the current dose, discontinue from the trial, or escalate to the next higher dose. Patients not experiencing dose-limiting toxicity continued escalating for 3 weeks until they reached a target dose of 200 mg daily, either once or twice daily, or placebo as randomized. Patients who could not tolerate dose escalation maintained the maximum tolerated dose of 25 mg, 50 mg, or 100 mg for the remainder of their 12 weeks of treatment. Final efficacy assessments were made at the termination visit, and the study medication was discontinued following 12 weeks of drug treatment.

Blinding was rigorously maintained, as all patients took capsules morning and evening that were visually identical. There were no assessments or trial procedures that might have led to accidental unblinding.

Patient-reported outcome measures. Patients reported outcomes during the baseline and remaining study phases using multiple domains and methods. Three scales were used to assess pain: the Short-Form McGill Pain Questionnaire[22], the visual analog scale (VAS), and an Anchored Logarithmic Scale developed by Gracely and Kwilosz[23]. The Short-Form McGill Pain Questionnaire is a commonly used pain scale that can be used to assess different components of the experience of pain[22]. The VAS con-

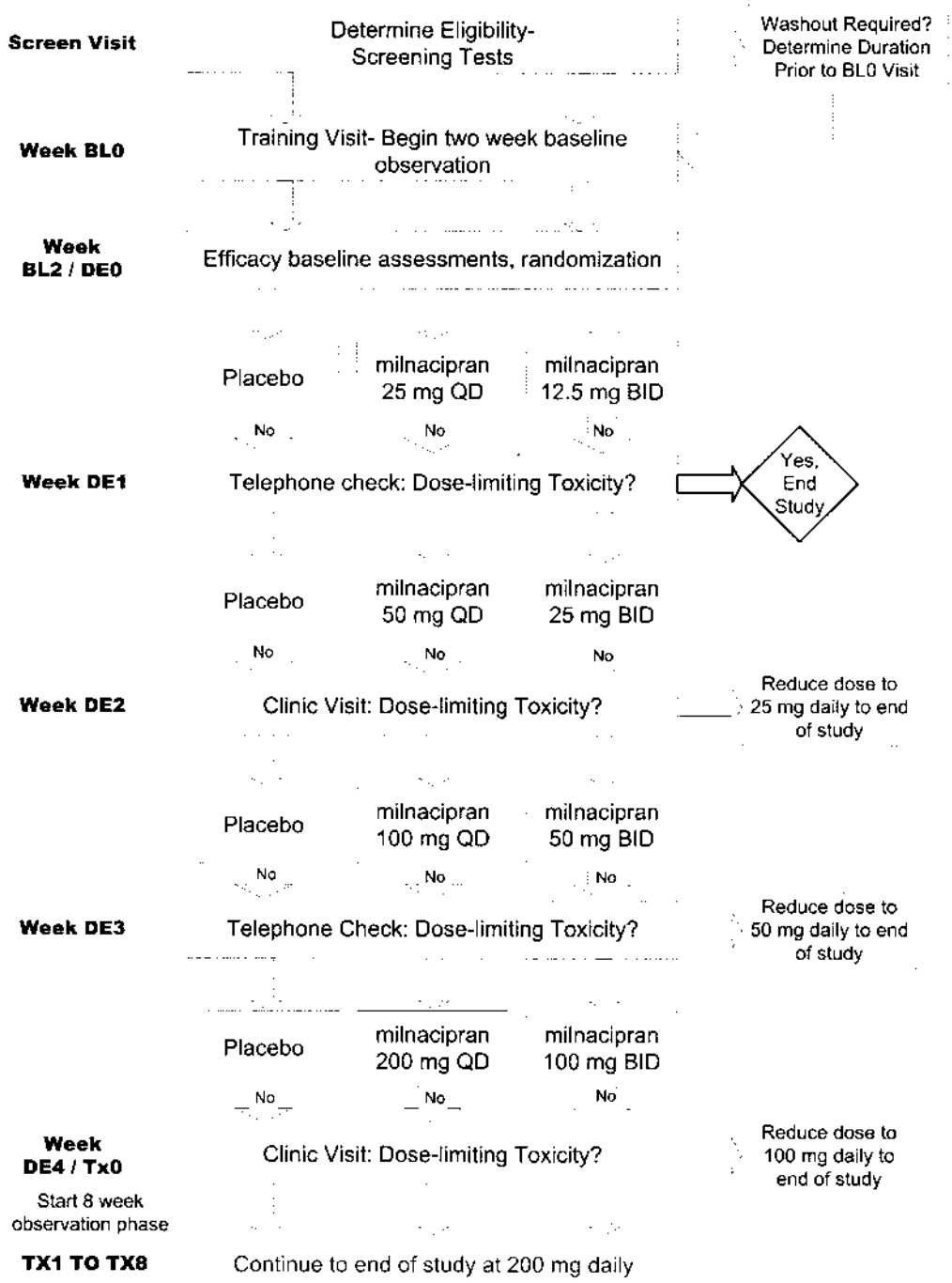

Figure 1. The schedule of milnacipran dosing and study activities. BID: twice daily dosing, QD: once daily dosing, BL: baseline phase, DE: dose escalation phase, TX: treatment phase, or stable-dose phase.

sisted of a simple 100 mm line with endpoints of "no pain" and "very severe pain" on which patients indicated symptom intensity. The Gracely scale was developed to account for the inherent logarithmic expression of many sensory responses. Like the VAS, the Gracely scale uses descriptive anchors spaced along the length of the scale. However, the Gracely scale allows one to measure changes in intensity over 2 logs, i.e., a 100-fold change in intensity. It is estimated that a decrease in 3.3 units in the Gracely scale corresponds to a 30% decrease in pain scores as measured by standard linear VAS, and 4 units in the Gracely scale corresponds to 50% decrease (unpublished observations).

Palm© based electronic diaries (e-diaries) were provided to all patients for the length of the study for the purpose of recording symptoms on a "real-time" basis. Patients were asked to rate their pain using the Gracely scale every morning (24-hour recall interval), every week (7-day recall interval), and in response to 4 to 6 prompts given randomly interspersed over the waking hours. These prompts were initiated by a sound cue from the diary, which could be terminated by entering a value for pain and/or by silencing the device. Real-time e-diaries were used because they eliminate

the bias involved in asking individuals to recall symptoms, and they improve compliance by prompting and time-date stamping each response[24]. Therefore, pain measures obtained from e-diaries were chosen to be the primary dependent variable for the measurement of pain improvement. In addition, patients also completed traditional paper assessments of pain and other measures at their monthly clinic visits.

At the end of the study, each patient was asked to complete the Patient Clinical Global Impression of Change, with queries about the status of his/her FM compared to the baseline assessment. Patients were asked to rate the change in their condition on a scale of 1 to 7, where 1 was "very much improved," 4 was "unchanged," and 7 was "very much worse." Additional assessments included the Fibromyalgia Impact Questionnaire (FIQ)[25], the Medical Outcomes Study Short Form-36 (SF-36)[26], the Jenkins sleep scale[27], and the Arizona Sexual Experiences Scale (ASEX)[28]. Sleep quality and quantity and quality of life were assessed both by e-diaries and by paper inventories. Adverse events and vital signs (temperature, standing and supine blood pressure, and pulse rates) were reported during monthly clinic visits.

Statistical analysis. The primary efficacy measure was the change of average daily pain scores recorded in the e-diary, comparing the final 2 weeks of the trial to the 2-week baseline period. A weekly average pain score was also calculated for each patient using the random-prompt pain score report, the daily recall pain score report, and the weekly recall diary pain score report. In addition to assessing the mean reduction in pain by treatment group, a binary responder analysis (using both a 30% and 50% reduction in pain as a definition of response) was also performed[29].

In an attempt to establish preexisting signs and symptoms, an FM signs and symptoms inventory was collected at the screening visit. Adverse events reported by study site were translated to preferred terms using a MedDRA dictionary[30]. Each individual adverse event was counted only once on the basis of the maximum intensity recorded, regardless of the number of times the patient reported the event.

Sample size calculations were performed assuming the 3:3:2 treatment allocation ratio, and assuming that roughly 50% of patients randomized to a milnacipran arm would escalate to the high-dose level. For planning purposes, the projected mean change in weekly average pain scores (calculated using either the daily or weekly pain score recorded on the e-diary) over baseline was assumed to be –20% for milnacipran and –4% for placebo. Last observation carried forward coupled with an intent-to-treat approach was used in all analyses other than the completer analyses. In the results, completer analyses are explicitly identified when performed. Continuous variables are analyzed with Student's t test while categorical endpoints are analyzed with Fisher's exact test. Nominal p values are displayed — each statistical hypothesis is assumed to be independent.

RESULTS

Study patients and demographics. A total of 184 patients were screened for inclusion in the study. Of these, 125 patients were enrolled in the study between March 20, 2002, and December 10, 2002, and then randomized to one of 3 treatment groups: milnacipran QD (46 patients), milnacipran BID (51 patients), or placebo (28 patients). Patient demographics are summarized in Table 1.

Table 1 indicates that subject demographics were similar between groups, with the exception of the prevalence of comorbid depression. Mean ages were similar among treatment groups, ranging from 46.2 to 48.0 years. The majority of patients in each treatment group were female (96% to 98%) and Caucasian (79% to 89%). The mean duration of FM ranged from 3.8 to 4.3 years among the 3 treatment groups. Most patients had experienced multiple treatment modalities prior to enrollment in the study, the most common being exercise (62%), hot-cold packs (60%), massage (50%), physical therapy or rehabilitation (34%), chiropractic treatment (30%), dietary changes (26%), and acupuncture and meditation (18% each). Eleven percent (11%) of patients had received psychotherapy, 9% stress management, and 5% psychiatric treatments.

Compliance and early terminations. Patient disposition is summarized in Figure 2. Seventy-two percent of enrolled patients completed the study, with no significant differences in dropout rates among the 3 groups (30.4%, 27.5%, and 25.0% in the milnacipran QD, milnacipran BID, and placebo groups, respectively). The most frequent reasons for discontinuation in the overall population were adverse events (14.4%) followed by therapeutic failure (8.8%; see below for detailed adverse event data). Among individuals who completed the trial, 95% of placebo, 81% of QD, and 92% of BID participants achieved dose escalation to the maximum dose of 200 mg. The mean daily dose of milnacipran was 174 mg in the QD participant group and 191 mg in the BID group.

Efficacy results: pain. As described above, information regarding patients' pain experience was collected using both electronic, real-time assessments and more traditional written recall measures. The primary outcome measure chosen *a priori* was the 2-week average daily pain score collected from the e-diary morning report. Secondary pain outcomes included changes in weekly pain score collected electronically, daily and weekly recall paper VAS and Gracely scales, and the McGill Present Pain Score (Table 2).

Binary responder analyses were also performed; these analyses classify patients into dichotomous groups of "pain responders" or "nonresponders" and were designed to detect clinically meaningful differences rather than merely statistically significant changes. However, such groupings depend on the use of potentially contentious criteria for determining responder threshold, and partial responses can be missed in the analysis if the threshold is set too high. In this trial, 2 different methods were used to define "pain responders": a 30% improvement in pain score and a 50% improvement in pain score over baseline. As described above, for Gracely scale measurements, a decrease of $\geq$ 3.3 units defined a 30% "responder," and a decrease of $\geq$ 4 units defined a 50% "responder."

As shown in Table 2, BID milnacipran was a more effective analgesic than QD milnacipran. Improvements in pain reached statistical significance for BID milnacipran on 9 of the 13 pain measures collected, whereas QD milnacipran results reached significance on none of the measures. Results also suggested that pain measures with longer recall (i.e., weekly electronic diary vs daily electronic diary) showed more significant improvements than measures collected in real-time or with shorter recall intervals.

Because we anticipated a differential response to therapy

Table 1. Demographics for patients receiving placebo or milnacipran dosed once daily (QD) or twice daily (BID).

Characteristic	Milnacipran BID, n = 51	Milnacipran QD, n = 46	Placebo, n = 28	Total, n = 125
Age, yrs				
Mean	47.4	46.2	48.0	47.0
SD	11.6	12.2	8.4	11.1
Minimum/maximum	20.0/68.0	19.0/69.0	24.0/63.0	19.0/69.0
Sex (%)				
Male	1 (2)	1 (2)	1 (4)	3 (2)
Female	50 (98)	45 (98)	27 (96)	122 (98)
Race (%)				
Caucasian	42 (82)	41 (89)	22 (79)	105 (84)
African American	3 (6)	1 (2)	1 (4)	5 (4)
Hispanic	5 (10)	4 (9)	3 (11)	12 (10)
Asian	0 (0)	0 (0)	1 (4)	1 (1)
Other	1 (2)	0 (0)	1 (4)	2 (2)
Duration of FM, yrs since diagnosis				
Mean	4.0	4.3	3.8	4.1
SD	3.8	4.8	3.7	4.2
Minimum/maximum	0.1/18.0	0.1/21.3	0.1/12.2	0.1/21.3
Comorbid depression (%)	8 (16)	3 (7)	9 (32)	20 (45)

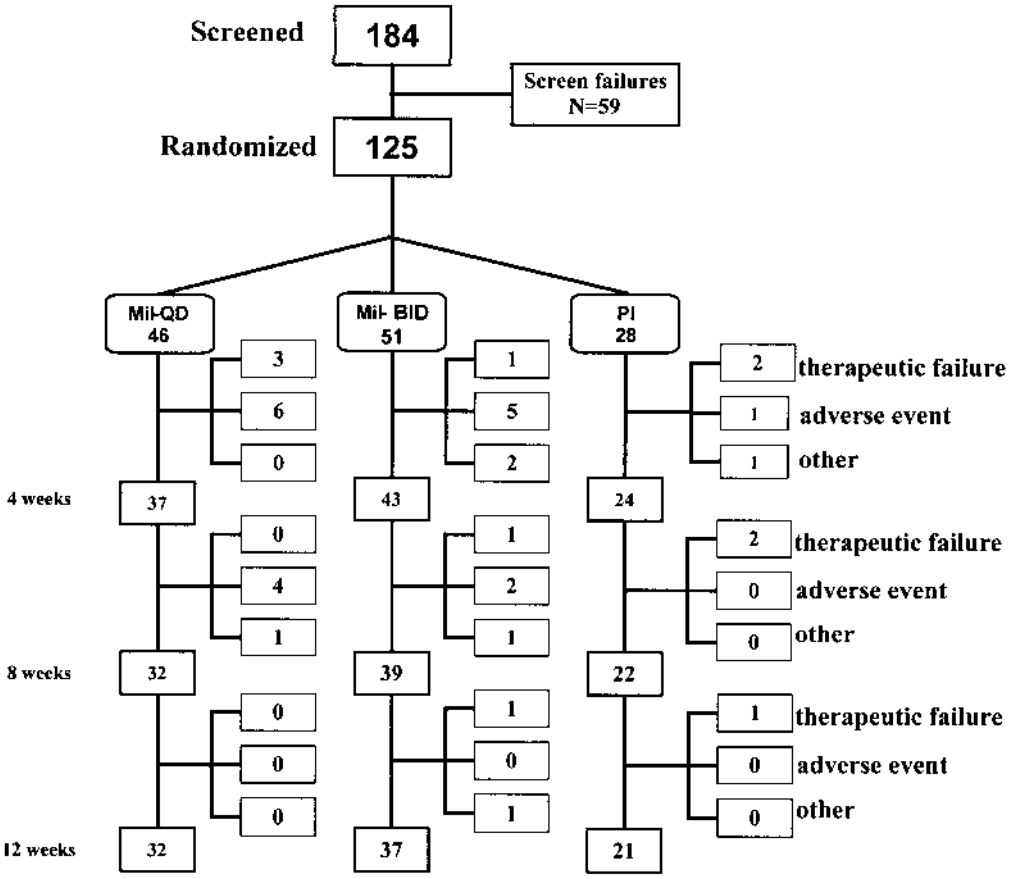

Figure 2. Number of patients screened and randomized into study groups; and number of patients reporting therapeutic failure, adverse events, or other issues at study Weeks 4, 8, and 12. Mil: milnacipran, Pl: placebo.

Table 2. Analyses of pain measures (intent to treat analyses using last observation carried forward method). A. Continuous pain measures, or mean change in pain measures from baseline less placebo change. B. Dichotomous pain measures, or the proportion of "responders" for each assessment.

A.	Milnacipran BID, n = 51 [p]	Milnacipran QD, n = 46 [p]	Placebo Score Change from Baseline, n = 28
Daily E-diary pain scores (0–20)	–3.0 ± 3.5 [0.191]	–2.2 ± 3.2 [0.635]	–1.86 ± 3.74
Weekly E-diary pain scores (0–20)	–3.1 ± 3.5 [0.025]	–2.5 ± 3.9 [0.139]	–1.14 ± 3.79
Paper Gracely pain scores (0–20)	–4.7 ± 4.8 [0.010]	–2.9 ± 4.8 [0.317]	–1.7 ± 4.1
Paper VAS pain scores (0–10)	–2.5 ± 2.8 [0.030]	–2.0 ± 3.2 [0.180]	–0.9 ± 2.9
McGill present-pain intensity (0–10)	–2.2 ± 2.7 [0.023]	–1.4 ± 3.2 [0.315]	–0.6 ± 2.7
B.	**BID, n = 51 (%) [p]**	**QD, n = 46 (%) [p]**	**Placebo, n = 28 (%)**
Daily E-diary proportion of responders			
30% pain reduction (≥ –3.3 units)	18 (35) [0.125]	10 (22) [0.772]	5 (18)
50% pain reduction (≥ –4.0 units)	18 (35) [0.066]	10 (22) [0.546]	4 (14)
Weekly E-diary proportion of responders			
30% pain reduction (≥ –3.3 units)	20 (39) [0.023]	13 (28) [0.255]	4 (14)
50% pain reduction (≥ –4.0 units)	19 (37) [0.040]	10 (22) [0.550]	4 (14)
Paper Gracely pain scores			
30% pain reduction (≥ –3.3 units)	23 (45) [0.007]	16 (35) [0.183]	5 (18)
50% pain reduction (≥ –4.0 units)	19 (37) [0.040]	13 (28) [0.250]	4 (14)
Paper VAS pain scores			
30% pain reduction (≥ –3.3 units)	20 (39) [0.136]	16 (35) [0.297]	6 (21)
50% pain reduction (≥ –4.0 units)	15 (29) [0.595]	12 (26) [0.783]	6 (21)

in depressed and nondepressed patients, further analyses were performed examining this issue. MINI results were used for identifying the presence of comorbid depression. As noted, randomization did not equally distribute depressed individuals among the 3 groups. The rate of comorbid depression for those randomized to BID milnacipran was 16%, for QD milnacipran 7%, and for placebo 32%. Thus, as a percentage of participants, more placebo patients had comorbid major depression disorder than either milnacipran group.

Statistically greater improvements in pain reduction were seen in nondepressed patients versus depressed patients treated with milnacipran. However, this difference did not occur because milnacipran was more effective among nondepressed patients, but rather because the placebo response rate was considerably higher among depressed patients. This is exemplified in Table 3, which presents the results of a binary responder analysis for BID milnacipran using e-diary assessment data. In response to placebo, 44% of depressed patients (vs 0% of nondepressed patients) reported a 50% reduction in pain on daily assessments, and 33% of depressed patients (vs 5% of nondepressed patients) reported a 50% reduction in pain on weekly assessments. Similar findings were noted for other pain measures, as well as for most other outcomes (data not shown).

Table 4 shows the same continuous pain measures as Table 2, but for nondepressed participants only. As would be expected from the different placebo response rates, there were significantly greater decreases in pain score between treated and placebo participants in this nondepressed subset as compared to the total group.

Efficacy results: other measures. Patients' global assessment of their clinical improvement during the trial was an important secondary outcome measure. Among individuals who

Table 3. 50% pain responders* taking milnacipran BID by baseline major depressive episode (MDE) status (intent to treat analyses using last observation carried forward method).

	All Patients, n (%) [p]	MDE Patients, n (%) [p]	Non-MDE Patients, n (%) [p]
Daily E-diary 50% pain reduction			
Milnacipran BID	18 (35) [0.066]	2 (25) [NS]	16 (37) [0.001]
Placebo	4 (14) —	4 (44) —	0 (0) —
Weekly E-diary 50% pain reduction			
Milnacipran BID	19 (37) [0.040]	3 (38) [NS]	16 (37) [0.012]
Placebo	4 (14) —	3 (33) —	1 (5) —

* ≥ 4.0 unit reduction on Gracely pain scale.

Table 4. Continuous pain measures (nondepressed FM patients only). Intent to treat analyses using last observation carried forward method. Mean change from baseline in pain measures less placebo change.

	Milnacipran BID, n = 43 [p]	Milnacipran QD, n = 43 [p]	Placebo Score Change from Baseline, n = 19
Daily E-diary pain scores (0–20)	–3.0 [0.013]	–2.2 [0.081]	–0.94
Weekly E-diary pain scores (0–20)	–3.1 [0.001]	–2.4 [0.018]	–0.23
Paper Gracely pain scores (0–20)	–4.7 [0.002]	–2.5 [0.110]	–0.7
Paper VAS pain scores (0–10)	–2.5 [0.006]	–1.8 [0.092]	–0.4
McGill present-pain intensity (0–10)	–2.0 [0.014]	–1.2 [0.192]	–0.1

completed the trial, those who received either BID or QD milnacipran were significantly more likely than those who received placebo to rate themselves as improved (73% BID, 77% QD, 38% placebo; p = 0.013 for BID milnacipran vs placebo, p = 0.008 for QD milnacipran patients versus placebo; Figure 3).

A number of other secondary outcome measures were assessed, using the FIQ, SF-36, Jenkins Sleep Scale, and ASEX. Because the above evidence indicated that BID milnacipran was a more effective analgesic than QD milnacipran, the analysis of these other secondary outcome measures focused on the BID milnacipran dose. On the FIQ, patients taking BID milnacipran reported significant improvement in "feel good" at the p = 0.05 level (p = 0.038), improvement in physical function at the trend level (p = 0.074), and a nonsignificant trend toward improvement in the FIQ total score (p = 0.188). Not surprisingly for a 12-week trial, there was no effect of BID milnacipran on job performance or absenteeism. The FIQ also contains a series of VAS scores, and the BID milnacipran group had statistically significant improvements in pain (p = 0.032), fatigue (p = 0.032), and morning stiffness (p = 0.047) compared to the placebo group, with trends toward improvement in depression and anxiety (Figure 4). There were also nonsignificant improvements in self-reported physical function for patients taking BID milnacipran as measured by the Physical Component summary score on the SF-36 (p = 0.124). Similarly, nonsignificant improvements were seen in sleep as measured by the Jenkins composite score (p = 0.229). Sexual function, as measured by the ASEX, improved equally in BID milnacipran and placebo-treated patients.

Safety and tolerability results. No unexpected safety concerns arose from this trial. There were no serious adverse events, and 88% of reported adverse events were rated as mild or moderate in severity. No patient discontinued due to clinically significant laboratory abnormalities. Consistent with previous trial results involving depressed patients, 7% of milnacipran-treated patients versus 4% of placebo-treated experienced mild elevations in alanine transferase and/or aspartate transferase, although no patient experienced elevations above 2 times the upper limits of normal, and no

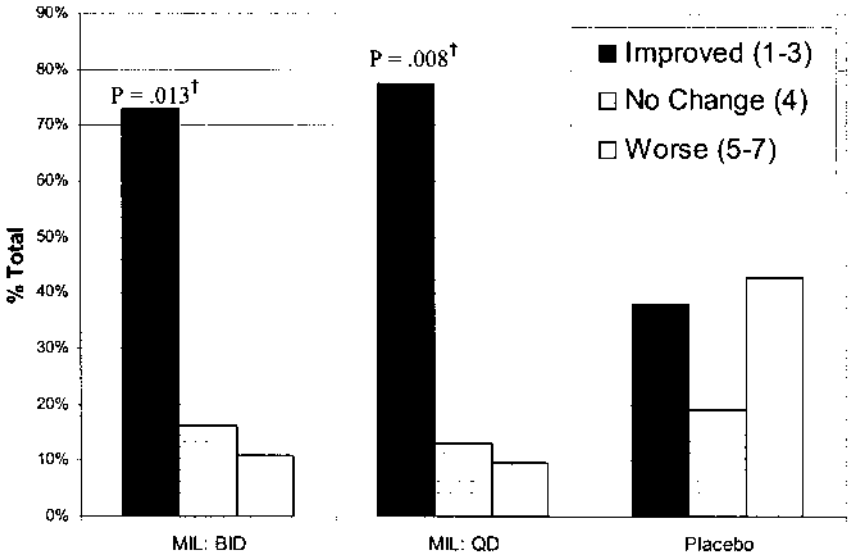

Figure 3. Self-report of change in overall status. Patients were asked to assess their global impression of change in FM severity over the course of the study. The percentage of patients completing the trial who thought they improved, got worse, or experienced no change is illustrated. †Milnacipran (MIL) vs placebo.

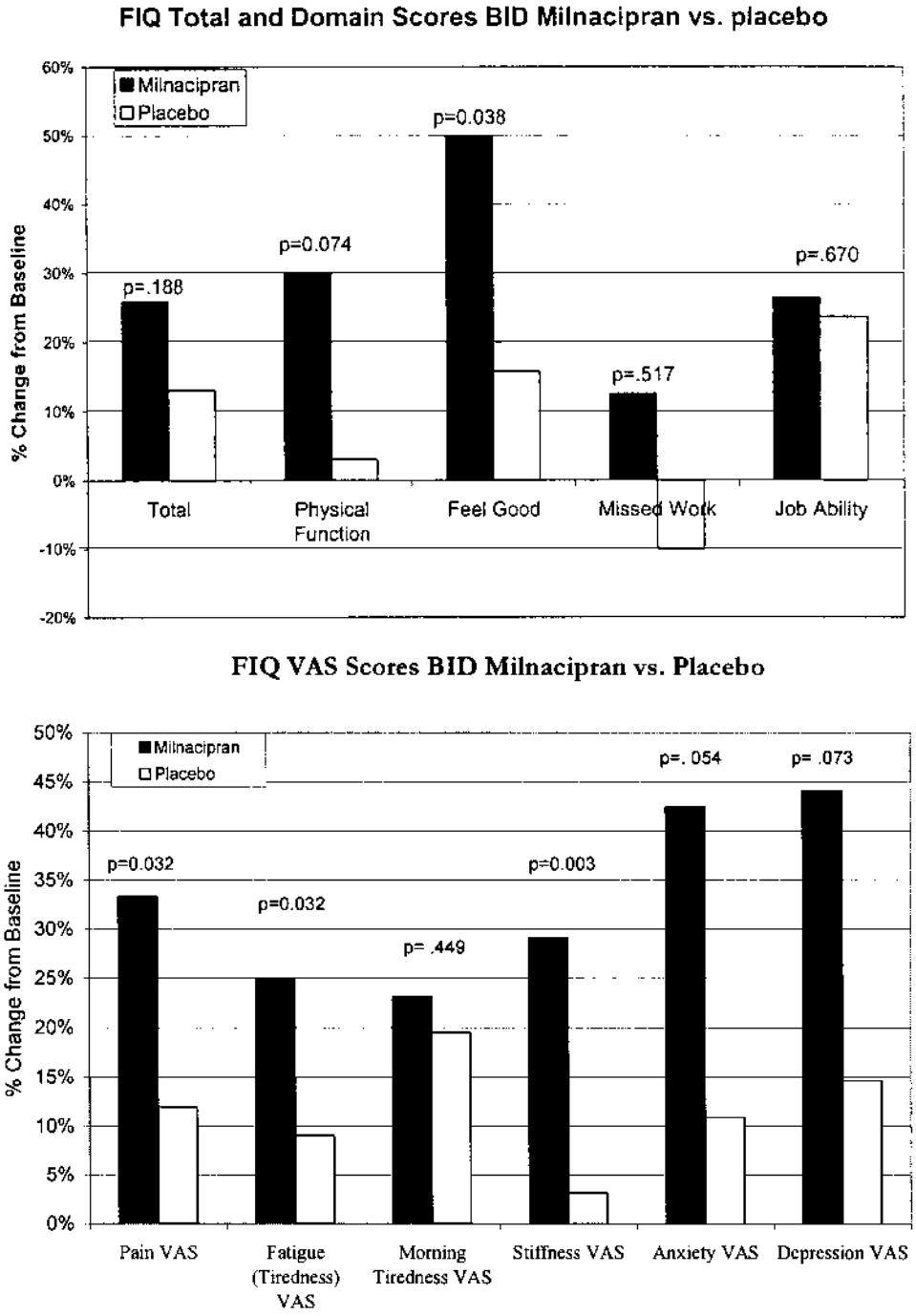

Figure 4. Scores from the Fibromyalgia Impact Questionnaire (FIQ) were used to determine between-group changes in non-pain outcomes among patients completing the trial, including the total FIQ score, specific domain scores, and visual analog scale (VAS) scores.

patient experienced any concomitant elevation in alkaline phosphatase or bilirubin.

Overall, 14.4% of patients discontinued the study prior to endpoint due to adverse events, including 13.7% of patients receiving BID milnacipran (7 patients), 21.7% of patients receiving QD milnacipran (10 patients), and 3.6% of patients receiving placebo (one patient). The majority (67%) of discontinuations secondary to adverse events occurred during the first 4 weeks of the trial, while patients were undergoing dose escalation. Headache and gastrointestinal (GI) complaints (nausea, abdominal pain, increased GI upset, and constipation) were the most frequent reasons stated for early termination. Other reasons for discontinuation included orthostatic dizziness, exacerbation of hypertension,

depression, lethargy, increased sweating, and hot flashes. One patient experienced a moderate exacerbation of preexisting hypertension that precluded dose escalation above 50 mg milnacipran BID, and led to early termination at Day 28. A second patient halted dose escalation at 50 mg milnacipran BID due to moderate postural dizziness, later discontinuing at Day 35 for persistence of this effect. Two milnacipran-treated patients discontinued due to depression, the first of whom had both a history of depression and a diagnosis at screening of current major depressive episode (MDE), as determined by the MINI. This patient discontinued after 13 days on study drug due to worsening depression, while receiving 50 mg milnacipran QD. The second patient had a history of depression, but was not MDE-positive at screening. She terminated from the trial after 35 days of treatment due to depressive episode, nausea and headache, after escalating to only 25 mg milnacipran QD.

Cardiovascular adverse events reported among the 97 milnacipran-treated patients included 6 reports of palpitations (5 mild, one moderate severity), 6 reports of postural dizziness (5 mild, one moderate), 2 reports of moderate exacerbation of hypertension, and one report of moderate increased heart rate upon standing. As described above, 2 of these patients discontinued early from the trial — one due to an exacerbation of hypertension and the other due to postural dizziness.

Previous trials indicated that milnacipran induces mild to moderate increases in mean pulse rates (+3 to +8 bpm), and our results were comparable. Mean blood pressure among milnacipran treatment groups showed a slight increase, ranging from 1.5 to 3.4 mm Hg for supine systolic pressures (–1.1 to 2.7 mm Hg in the placebo group) and 2.6 to 3.7 mm Hg for supine diastolic pressures (–3.5 to 1.2 mm Hg in the placebo group). These changes were not statistically different among treatment groups. Two milnacipran-treated patients (2.1%) reported exacerbation of hypertension. Both patients had preexisting hypertension and were receiving antihypertensive drug therapy.

A specific focus of this trial was the tolerability of high-dose (200 mg daily) milnacipran. Among patients who completed the 12-week study, 92% of BID and 81% of QD milnacipran-treated patients were successfully escalated to 200 mg daily. Only 9 milnacipran patients who completed the study (6 QD and 3 BID) were taking doses less than 200 mg daily. In addition to the greater rate of intolerance in the QD group, the higher incidence of adverse events, as well as the higher dropout rate due to adverse events, suggested that once-daily dosing was not as well tolerated as twice-daily dosing. Most notable was the increased incidence of nausea, abdominal pain, constipation, dizziness, postural dizziness, hot flushes/flushing, and palpitations among QD patients. Together, these observations suggest that for the larger doses, BID dosing is better tolerated, and peak drug level may be a significant factor in the generation of certain adverse effects.

DISCUSSION

Administration of milnacipran to patients with FM led to significant improvements in global well being, fatigue, (some measures of) pain, and a variety of related symptom domains. Twice-daily milnacipran had significantly better analgesic properties than once-daily milnacipran. Milnacipran was generally well tolerated, especially with BID dosing. The majority of adverse events were rated as mild or moderate, and no serious adverse events were reported.

Even though this drug has antidepressant properties, there was a greater statistical improvement noted in nondepressed FM patients than in those with FM and comorbid depression. This increased effect size did not occur because milnacipran was more efficacious in nondepressed patients (37% of nondepressed vs 38% of depressed patients experienced a 50% reduction in pain on weekly e-diary assessments), but instead, because of a much higher placebo response among depressed FM patients (33%) compared to nondepressed (5%). Thus, although milnacipran was originally developed as an antidepressant, it does not appear that the analgesic and other beneficial effects in FM occur strictly on the basis of improvements in mood. This is consistent with other classes of compounds, such as tricyclics, where analgesic effects are somewhat or largely independent of antidepressant effects[13,31-33].

In addition to demonstrating efficacy on most measures of pain, a significant proportion of the patients randomized to milnacipran showed improvement across a number of other symptom domains. Statistical differences between BID milnacipran and placebo were noted in physical functioning, fatigue level, and degree of reported physical impairment. Nonsignificant trends toward improvement were found on many other domains. Sleep was the one common symptom of FM that did not show evidence of significant improvement. This is not surprising, since milnacipran is an "activating" agent, presumably because of its noradrenergic effects. However, it is important to note that there were no detrimental effects on sleep.

The most striking evidence of a beneficial effect of milnacipran treatment in this trial was in the patient global outcome measure. Over 70% of completers in both milnacipran treatment groups reported an improvement in their overall status, while only 10% reported worsening. In the placebo arm, the most frequent category reported was "worsening," with over 40% of the placebo patients who completed the trial rating themselves as worse at endpoint. It is conceivable that milnacipran improved many of the symptoms of FM, and that this outcome measure essentially represents a summation of those improvements.

Because this was one of the first phase II trials conducted for FM, a greater number of outcomes were collected

than would ordinarily be collected in a typical randomized, controlled trial. In particular, pain was assessed using a variety of different methodologies. A rich body of literature suggests that asking individuals to recall their pain and other symptoms introduces many biases, and that even paper-and-pencil diaries, which theoretically sample symptoms on a real-time basis, are fraught with compliance problems[34]. E-diaries have the advantage of increased accuracy because these methods use electronic time-stamps that ensure patients actually record their symptoms at the requested time, rather than "backward-filling" (completing several days' worth of diaries at once) or "forward-filling" (completing diaries in advance of the time the symptom is asked to be recorded) their diaries[23,34-36].

We found that the pain results collected on e-diaries generally revealed less significant differences between milnacipran and placebo groups than the classic written instruments completed at the clinic visits. Further studies will be necessary to determine if this is a consistent finding when comparing these 2 methods of data collection, or if this effect is unique to this drug or to this trial. Because milnacipran led to a global improvement in many symptoms and in overall well being, it is possible that patients who were asked to recall their pain over a longer interval were positively influenced by their overall improved status. This would be consistent with previous reports that recall measures of pain report are highly influenced by how the individual feels at the time he/she completes the instrument (i.e., if he/she has worse pain or is depressed, he/she will record higher recall pain values, and vice-versa) rather than being a true "average" of how the individual feels over the recording interval[37].

The presence of 11/18 tender points on physical examination is part of the ACR diagnostic criteria for FM[1], and all study participants received a tender point count to verify that they met ACR criteria for FM prior to enrollment. However, a tender point count was not used as part of outcomes assessment, because tender points may not reflect changes in pain sensitivity/processing[38,39], and because tender points are strongly influenced by patient distress[38,39]. Because of this, any improvements in tender point count in our trial would likely be strongly influenced by milnacipran's known effects on psychological function, whereas the focus of the trial was milnacipran's analgesic properties.

The difference in the analgesic effect of BID and QD milnacipran was unexpected. It is possible that the mechanisms and the pharmacology by which milnacipran provides analgesia may be different from the processes by which milnacipran benefits other symptoms of FM, as both QD and BID milnacipran patients reported similar global improvement scores. It is possible that QD patients may have had inadequate drug levels of milnacipran at the end of the day (the half-life is 6–8 hours), and this may have contributed to the less effective pain relief.

From a safety perspective, milnacipran was generally well tolerated by the study population, especially in patients who received their daily milnacipran in split dosage (BID). By design, the trial allowed patients to stop the dose escalation process prior to reaching the maximum dose of 200 mg daily because there was an expectation of potentially serious high-dose drug intolerance. However, 92% of BID patients who completed the trial escalated to the maximum dosage, with little evidence of persistent dose intolerance or late-onset adverse effects. The majority of adverse events recorded were transient and mild to moderate in severity, and no serious adverse events were recorded.

Although it is difficult to compare the clinical benefit of one drug to another except if the 2 drugs are directly compared in a clinical trial, these data allow some preliminary sense of their efficacy for FM. For pain relief, for example, Arnold, *et al* performed a metaanalysis of randomized controlled trials of tricyclics in FM, and determined that the overall effect size was 0.52, in the moderate range[40]. This is very similar to the effect size seen for pain relief in our trial (0.48 for pain diary, 0.52 for paper-and-pencil VAS).

Milnacipran dosed BID at 200 mg per day was an effective analgesic for the symptom of pain in patients with FM, and had beneficial effects on a wide range of FM symptoms, including fatigue, physical function, and quality of life. In addition, patients taking milnacipran dosed either QD or BID reported significantly improved global clinical improvement. This medication did not appear to be acting solely as an antidepressant, because impressive separation between drug and placebo treated patients was noted in nondepressed patients. As with any initial trial, further studies with variable dosages and larger numbers of patients are needed to support and extend these findings.

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The Relationship Between Depression, Clinical Pain, and Experimental Pain in a Chronic Pain Cohort

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Objective. **Individuals with chronic pain frequently display comorbid depression, but the impact of symptoms of depression on pain processing is not completely understood. This study evaluated the effect of symptoms of depression and/or clinically diagnosed major depressive disorder (MDD) on pain processing in patients with fibromyalgia (FM).**

Methods. **Results of quantitative sensory testing and neural responses to equally painful pressure stimuli (measured by functional magnetic resonance imaging [fMRI]) were compared with the levels of symptoms of depression and comorbid MDD among patients with FM.**

Results. **Neither the level of symptoms of depression nor the presence of comorbid MDD was associated with the results of sensory testing or the magnitude of neuronal activation in brain areas associated with the sensory dimension of pain (primary and secondary somatosensory cortices). However, symptoms of depression and the presence of MDD were associated with the magnitude of pain-evoked neuronal activations in brain regions associated with affective pain processing (the amygdalae and contralateral anterior insula). Clinical pain intensity was associated with measures of both the sensory dimension of pain (results of sensory testing) and the affective dimension of pain (activations in the insula bilaterally, contralateral anterior cingulate cortex, and prefrontal cortex).**

Conclusion. **In patients with FM, neither the extent of depression nor the presence of comorbid major depression modulates the sensory-discriminative aspects of pain processing (i.e., localizing pain and reporting its level of intensity), as measured by sensory testing or fMRI. However, depression is associated with the magnitude of neuronal activation in brain regions that process the affective-motivational dimension of pain. These data suggest that there are parallel, somewhat independent neural pain-processing networks for sensory and affective pain elements. The implication for treatment is that addressing an individual's depression (e.g., by prescribing an antidepressant medication that has no analgesic properties) will not necessarily have an impact on the sensory dimension of pain.**

Major depressive disorder (MDD) is often found in conjunction with chronic pain, with a prevalence of 30–54% among tertiary care patients (1). Hypotheses about the link between MDD and chronic pain include the notion that one causes the other, or that a common underlying diathesis causes individuals to be more susceptible to both MDD and chronic pain (2). Laboratory studies assessing this relationship have yielded inconsistent results, showing increased experimental pain thresholds (3), decreased experimental pain tolerance (4), or no relationship between experimental pain threshold and symptoms of depression (5).

Although the underlying mechanism mediating the comorbidity between MDD and chronic pain is unknown, there is support for a biologic model (i.e., involvement of neurotransmitters such as serotonin, norepinephrine, corticotropin-releasing hormone, and substance P in both chronic pain and MDD), as well as a psychosocial model (i.e., association of sadness or

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maladaptive responses such as catastrophizing or learned helplessness with both chronic pain and MDD).

Pain is a multidimensional experience with both sensory-discriminative and affective-motivational dimensions (6,7). Studies investigating the underlying structure of pain descriptors and pain responses consistently include at least 2 factors that reflect both the sensory and the affective/evaluative dimensions of pain (8).

Stimulation-induced pain consistently increases neural activity in a network of brain structures involved in processing sensation, movement, emotion, and cognition (9–11). Evidence from functional brain imaging and studies of clinical lesions supports a division between brain regions such as the primary and secondary somatosensory cortices (S1 and S2) that process the sensory-discriminative dimension of pain (12), and regions such as the anterior insula and anterior cingulate that process the affective and evaluative dimensions of pain (13,14).

Brain imaging studies in patients with depression have shown reduced cerebral blood flow, specifically in the prefrontal cortex, anterior cingulate gyrus, anterior temporal cortex, caudate, putamen, and thalamus (15–18). The decreased blood flow in specific areas can be reversed with antidepressant therapy (19,20).

Fibromyalgia (FM) is a chronic pain syndrome with a prevalence from 0.5% to 4% in industrialized countries (21). The American College of Rheumatology (ACR) 1990 criteria for the classification of FM require both a history of chronic widespread pain and tenderness to blunt pressure (22). Since these patients often have comorbid depression, FM may be an ideal condition in which to study the relationship between MDD, clinical pain, and experimental pain.

This study evaluated 1) whether higher levels of symptoms of depression (or the presence of comorbid major depression) are associated with increased sensitivity to experimental pressure-induced pain, and 2) which brain areas are involved in mediating the relationship between experimental pain, levels of symptoms of depression, and clinical pain.

PATIENTS AND METHODS

Patients and groups. The study was conducted in the Georgetown University Medical Center General Clinical Research Center, a tertiary health care facility. Written informed consent was obtained from all study participants, and the study was approved by the Georgetown University Institutional Review Board. To be included in the FM cohort, patients had to meet the 1990 ACR criteria for FM (22). Exclusion criteria for all subjects were severe physical impairment, medical conditions that were capable of causing patients' symptoms (e.g., morbid obesity, autoimmune/inflammatory diseases, cardiopulmonary disorders), uncontrolled endocrine or allergic disorders (i.e., hyper-/hypothyroidism, diabetes, allergic rhinitis), malignancy, severe psychiatric illnesses (e.g., schizophrenia, substance abuse), factors known to affect the hypothalamic-pituitary-adrenal axis or autonomic function (cigarette smoking, daily caffeine intake exceeding the equivalent of 2 cups of coffee), and medication usage other than as-needed analgesics (excluding long-term narcotics) or appropriate dosages of thyroid hormone.

Fifty-three patients (33 female/20 male) and 42 controls (20 female/22 male) were included in the study. The mean ± SD age in the patient group and in the control group was 42 ± 9 years and 38 ± 9 years, respectively. Enrolled subjects were asked to discontinue intake of antidepressant medications 4 weeks prior to the study (depending on the half-life of the drug), but subjects were allowed to take nonsteroidal antiinflammatory medications as analgesics 3 days prior to the study. On day 1 of the study, patients completed self-report questionnaires, underwent the structured clinical interview, and were familiarized with the pain-testing paradigm. On day 2, experimental pain testing and functional magnetic resonance imaging (fMRI) were performed.

Clinical pain. Clinical pain was measured using a 100-mm visual analog scale (VAS). The 2 anchors for this VAS were 0 = no pain, and 100 = worst pain imaginable. Patients gave their responses verbally.

Center for Epidemiological Studies Depression Scale (CES-D). The CES-D is a 20-item, self-report questionnaire (23) that assesses symptoms of depression in nonpsychiatric adults. This was administered to patients to measure the extent of their symptoms of depression.

Composite International Diagnostic Interview (CIDI). The CIDI is a standardized instrument for assessment of mental disorders, with classifications according to the definitions and criteria of the International Classification of Diseases, Tenth Revision and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (24). Trained research assistants administered the 12-month computer version of the CIDI.

Sensory testing. Pressure-pain sensitivity was evaluated by subjective scaling of both the pain threshold level and more intense, suprathreshold pressure-pain sensations. Discrete 5-second pressure stimuli were applied to the left thumbnail by a 1-cm^2 hard rubber probe. Subjects rated the intensity of pressure-pain sensations using a combined numeric analog descriptor scale (25). During pain testing, a series of stimuli was presented in a predictable, ascending manner, beginning at 0.5 kg/cm^2 and increasing in 0.5-kg/cm^2 intervals to tolerance or to a maximum of 10 kg/cm^2. Following the ascending series, 36 stimuli were delivered at 20-second intervals in random order using the multiple random staircase (MRS) method (26). The MRS method determines the stimulus intensities necessary to elicit faint (0.5 of 20), moderate (7.5 of 20), and slightly intense (13.5 of 20) pain ratings. The MRS provides a relatively pure sensory-physiologic measure of experimental pain sensitivity (27,28).

Functional imaging. MRI and fMRI scans were performed on a 1.5-Tesla vision system (Siemens, Munich, Germany). A T1-weighted MRI anatomic scan session (time to echo [TE] 4 msec, time to recovery [TR] 9.7 msec, flip angle 12°, 256 × 256-pixel matrix, field of vision [FOV] 256 mm,

Table 1. Demographic and clinical characteristics of the control subjects and fibromyalgia (FM) patients*

	Controls (n = 42)	FM patients (n = 53)
Sex, no. male/no. female	22/20	20/33
Age, years	37.9 ± 9.1	42.0 ± 8.9
CES-D score	6.5 ± 6.6	17.1 ± 10.6†
Clinical pain VAS score	3.3 ± 10.1	47.5 ± 25.6†
Pressure-pain intensity, kg‡		
MRS low	1.81 ± 1.47	1.05 ± 0.73§
MRS medium	4.57 ± 2.39	2.96 ± 1.57¶
MRS high	6.99 ± 2.97	5.15 ± 2.53§

* Except where indicated otherwise, values are the mean ± SD. CES-D = Center for Epidemiological Studies Depression Scale; VAS = visual analog scale; MRS = multiple random staircase (method).
† $P < 0.001$ versus controls.
‡ Low = intensity needed to elicit first pain (pain threshold); medium = intensity needed to elicit moderate pain; high = intensity needed to elicit slightly intense pain.
§ $P < 0.05$ versus controls.
¶ $P < 0.01$ versus controls.

1-mm^3 voxels, acquired noninterleaved in the sagittal direction) was followed by 2 functional scan sessions using multislice echo-planar imaging fMRI acquisition (TE 40 msec, TR 5 seconds, flip angle 90°, 64 × 64-pixel matrix, FOV 192 mm, 50 horizontal 3-mm slices). These parameters allowed coverage of the entire brain with 3-mm^3 voxels.

During each functional scan session, the brain was scanned at 5-second intervals. Three initial scans allowed for saturation of the tissue. Starting on the fourth scan, pressure stimuli of 25 seconds' duration (the "on" condition) were alternated with 25-second resting periods (the "off" condition). Onset and offset of a stimulus was coincident with the beginning of a scan, allowing the acquisition of 5 scans during each of 12 "on" and 12 "off" conditions.

During the "on" conditions, stimuli of varying intensities were presented randomly. These stimulus intensities included 3 stimuli calibrated to elicit a rating of 13.5 of 20 (slightly intense pain). The analysis compared the scans acquired during these slightly intense pain conditions to those acquired during the "off" condition.

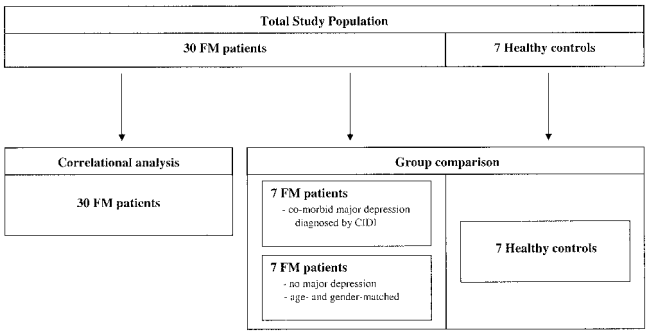

Figure 1. Outline of study design, including main correlational analysis and group comparisons. FM = fibromyalgia; CIDI = Composite International Diagnostic Interview.

Table 2. Correlation coefficients for associations between evoked pain sensitivity (MRS method), level of symptoms of depression, and magnitude of clinical pain in 53 fibromyalgia patients*

	MRS pressure-pain intensity			VAS pain score
	Low	Medium	High	
CES-D score				
r	−0.20	0.01	−0.11	0.26
P	0.20	0.97	0.50	0.06
VAS pain score				
r	−0.20	−0.18	−0.30	–
P	0.20	0.26	0.054	–

* Associations are Pearson correlation coefficients. See Table 1 for definitions.

Imaging analysis. Imaging data were analyzed with MEDx 3.4 (Sensor Systems, Sterling, VA). The functional images were corrected for head motion and intensity differences, and were spatially smoothed at 6-mm full width at half maximum.

The brain volumes collected during "on" conditions were compared by *t*-test to the brain volumes collected during "off" conditions. Resultant Z-statistic volumes and mean differences of the volumes were registered into standardized space using the SPM96 echo-planar imaging template and were then resliced to 2-mm^3 voxels.

Results were corrected for multiple comparisons (29). Anatomic regions were identified by inspection of individual functional images superimposed on an individual structural image, and by conversion of the coordinates to the coordinate system of the Talairach-Tournoux atlas and localization using this atlas (30) and automated software (31).

Table 3. Association of neuronal activations in brain regions with level of symptoms of depression and clinical pain ratings*

	Coordinates			Correlation with CES-D score		Correlation with VAS pain score	
Side, region	x	y	Z	r	Z	r	Z
Contralateral							
S1	56	−10	46	0.28	2.142	0.20	1.714
S2	66	−22	16	0.10	1.050	0.13	1.005
ACC	8	36	18	0.10	0.866	0.47†	3.540
Anterior insula	32	2	14	0.51†	4.085	–	–
Anterior insula	34	28	6	–	–	0.50†	3.818
PFC (BA 10)	32	50	23	0.06	0.547	0.53†	4.156
Amygdala	18	0	−10	0.40‡	3.091	0.13	1.005
Ipsilateral							
S2	−64	−20	14	0.20	1.714	0.21	1.985
Cerebellum	−34	−68	−30	0.10	1.134	0.10	0.987
Amygdala	−20	0	−12	0.50†	3.959	0.15	1.050

* Associations are Pearson correlation coefficients and Z statistics. Brain areas are mapped to the coordinate system of the Talairach-Tournoux atlas. S1 = primary somatosensory cortex; S2 = secondary somatosensory cortex; ACC = anterior cingulate cortex; PFC = prefrontal cortex; BA = Brodmann's area (see Table 1 for other definitions).
† $P < 0.05$, corrected for multiple comparisons.
‡ $P < 0.001$, uncorrected.

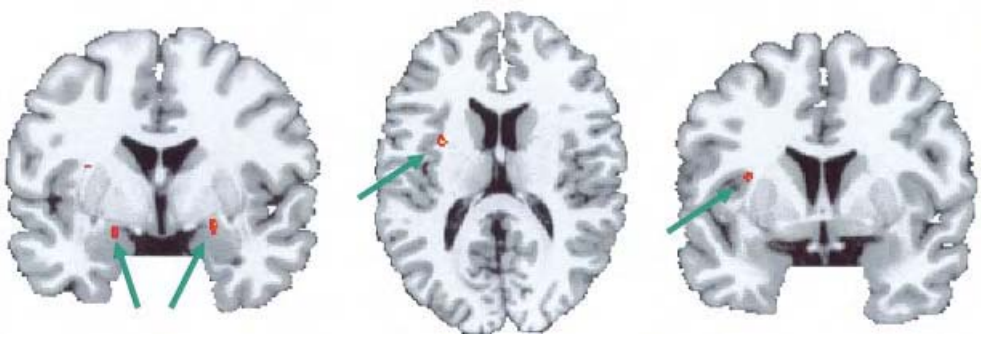

Figure 2. Brain regions associated with self-reported symptoms of depression. Pain-evoked neuronal activations were associated with self-reported level of symptoms of depression (**green arrows**). Regions of significant correlations are shown in standard space superimposed on a structural T1-weighted magnetic resonance image. Images are shown in radiologic view, with the right brain shown on the left. Higher levels of symptoms of depression were significantly associated with higher neuronal activation in both amygdalae (left image: x/y/z coordinates in Talairach space −20/0/−12 mm and 18/0/−10 mm) and in the contralateral anterior insula (middle and right images: x/y/z coordinates 32/2/14 mm).

Statistical analysis. Correlations between clinical pain, experimental pain sensitivity, and self-reported symptoms of depression were analyzed using Pearson's correlation coefficients (SPSS for Windows, version 11.0; SPSS, Chicago, IL). For the subset of patients who participated in the fMRI protocol, correlations in the mean difference of neuronal activation between no pain and slightly intense pain at each voxel of the brain and the extent of self-reported symptoms of depression or clinical pain were analyzed using Pearson's correlation coefficients, corrected for multiple comparisons.

RESULTS

Fifty-three patients with FM and 42 controls provided complete self-report data and participated in the experimental pain testing. The data from fMRI were collected on a subset of 30 patients with FM (18 female/12 male), with a mean age of 42 ± 10 years. The demographic and clinical data are shown in Table 1, and the study design is shown in Figure 1.

Associations between the magnitude of clinical pain, experimental pain sensitivity, and symptoms of depression for the patient group are shown in Table 2. The magnitude of clinical pain showed only weak correlations with self-reported symptoms of depression ($r = 0.26$, $P = 0.06$) and experimental pain ($r = -0.18$ to -0.30, $P = 0.26$–0.054). Pressure-pain thresholds at all pain intensity levels (i.e., mild, moderate, severe pain) were unrelated to self-reported symptoms of depression.

Results of the correlational analyses of self-reported symptoms of depression and neuronal activations are shown in Table 3 and Figure 2. Correlations

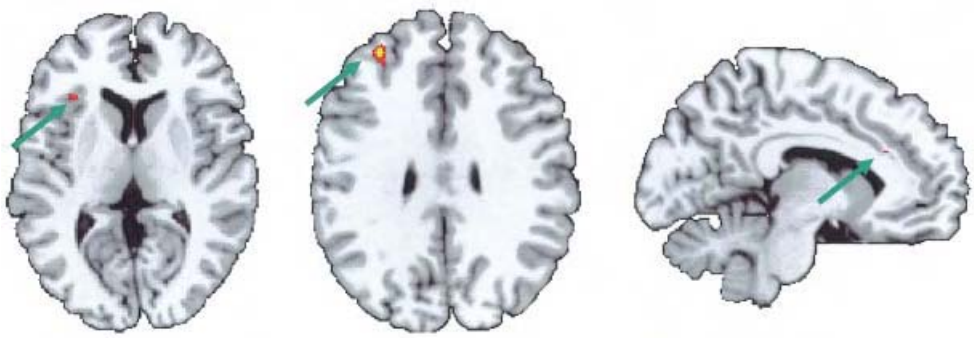

Figure 3. Brain regions associated with self-reported clinical pain score. Pain-evoked neuronal activations were associated with self-reported level of clinical pain (**green arrows**). Regions of significant correlations are shown in standard space superimposed on a structural T1-weighted magnetic resonance image. Images are shown in radiologic view, with the right brain shown on the left. Higher levels of clinical pain were significantly associated with higher neuronal activation in the anterior insula (left image: x/y/z coordinates in Talairach space 34/28/6 mm), the prefrontal cortex (middle image: x/y/z coordinates 32/50/23 mm), and the anterior cingulate (right image: x/y/z coordinates 8/36/18 mm).

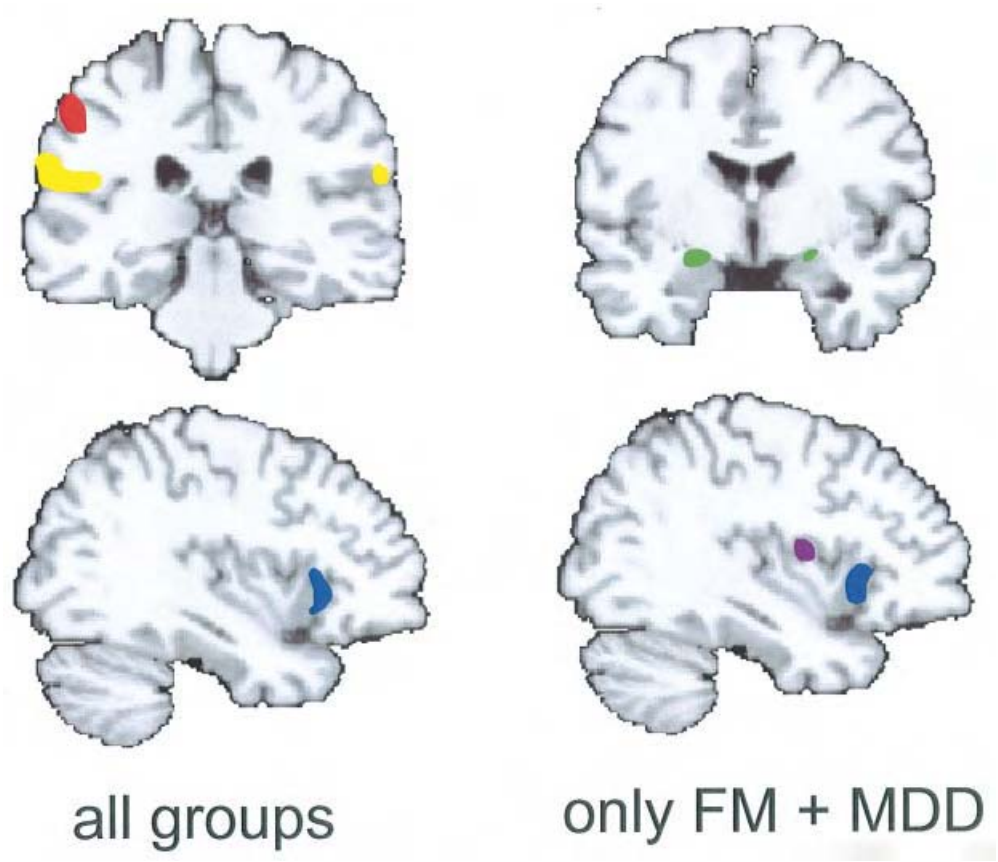

Figure 4. Between-group comparison of brain regions activated by pressure-pain stimuli. Pain-related neuronal activations were assessed in healthy controls, fibromyalgia (FM) patients without major depressive disorder (MDD), and FM patients with comorbid MDD. Regions of significant increases in neuronal activation are shown as colored areas superimposed on a structural T1-weighted magnetic resonance image. Images are shown in radiologic view, with the right brain shown on the left. Left images, Common neuronal activations in all 3 groups. Equally painful pressure stimuli at the left thumb result in common neuronal activations in all groups in the contralateral primary somatosensory cortex (red), secondary somatosensory cortex (yellow), and anterior insula (blue). Right images, Unique activations in FM patients with MDD after the same pressure stimuli. FM patients with MDD show additional activations in both amygdalae (green) and the anterior insula (purple).

with neuronal activations in cortical areas that process the sensory-discriminative dimension of pain (S1 and S2) were not significant. However, CES-D scores were significantly correlated with neuronal activations in the amygdalae and contralateral anterior insula.

Similar to the trends observed with the CES-D scores, clinical pain VAS scores reported by the subset of 30 FM patients did not correlate with neural activity in the S1 or S2 brain regions. The clinical pain scores, however, did correlate significantly with pain-evoked neural activity in the contralateral anterior insula, anterior cingulate cortex, and prefrontal cortex (Table 3 and Figure 3).

Self-reported symptoms of depression cannot be used to definitively diagnose MDD. In our sample of 30 FM subjects who underwent fMRI, a subset of 7 subjects met the full criteria for comorbid MDD by structured clinical interview (i.e., the CIDI). Therefore, in a second analysis, we compared fMRI patterns of neuronal activation in these 7 patients with those of 7 age- and sex-matched FM patients without MDD, and with 7 age- and sex-matched healthy control subjects (Figure 1). Consistent with previous studies in FM, both groups of FM patients, those with and those without MDD, required significantly less pressure to cause slightly intense pain as compared with the healthy controls (FM patients with no major depression 4.7 kg, FM patients with MDD 5.2 kg, controls 6.9 kg; $P < 0.001$ for both FM groups

versus controls) (32,33). These equally painful stimuli resulted in similar neuronal activations in the cortical areas that code for stimulus intensity in all 3 groups, and resulted in unique neuronal activations in both the amygdalae and the contralateral insula in the patients with MDD, thus confirming the results of the correlational analysis involving symptoms of depression, and extending the findings to the clinical diagnosis of MDD (Figure 4).

DISCUSSION

In a cohort of patients with chronic pain who had a confirmed diagnosis of FM, the level of symptoms of depression or presence of MDD was not associated with either subjective pressure-pain sensitivity or neuronal activations in regions of the brain that are implicated in processing the sensory-discriminative dimension of pain (i.e., S1 and S2). In contrast, the presence of MDD or symptoms of depression was associated with neuronal activation in brain regions implicated in processing the motivational-affective dimension of pain (i.e., the amygdalae and anterior insula). Clinical pain was related to both the sensory and the affective domains, in that it weakly correlated with sensory testing results and with the magnitude of neuronal activations in brain areas associated with affective/integrative aspects of pain processing (i.e., the insula bilaterally, the contralateral anterior cingulate cortex, and the prefrontal cortex).

These sensory testing and functional imaging data are consistent with the findings of a number of other studies suggesting that pain has at least 2 dimensions: a sensory-discriminative dimension that identifies its intensity, quality, and spatiotemporal characteristics, and an affective-motivational dimension that processes its negative valence and unpleasantness (6,7). These data also provide additional evidence that the anterior insula may play a critical role in integrating sensory and emotional experiences, since this was the only region associated with both symptoms of depression and the clinical pain report (34,35).

Much has been made of the overlap and similarities between pain and symptoms of depression, but these and other data suggest it is also important to identify pain-processing mechanisms that are independent of mood. For example, this and other functional imaging studies in FM suggest that there is objective evidence of amplification of the sensory dimension of pain that is totally independent of mood or emotion (32,36,37). Similar findings of allodynia/hyperalgesia that are not explained by psychological factors occur in other "central" pain syndromes, such as irritable bowel syndrome, temporomandibular disorder, and idiopathic low back pain (33,38).

The notion that sensory and affective aspects of pain may be independently processed is not just of theoretical interest. Dissimilar pharmacologic therapies may differentially influence the sensory and affective dimensions of pain (25). Within the class of antidepressants, some are relatively efficacious analgesics (e.g., tricyclic compounds), whereas others do not function in this manner (e.g., highly selective serotonin reuptake inhibitors) (39). The effects of antidepressants on pain also appear to be independent of mood, since 1) antidepressant effects and analgesic effects frequently occur independently of each other in clinical trials, and 2) doses of antidepressants necessary to produce analgesia are, in many cases, lower than the those required to treat MDD (40–44).

These data are consistent with a neuromatrix model of pain that applies concepts from cognitive neuroscience network theory (45). In this model, dimensions of the pain experience are the output of a neural network program, or neuromatrix, which is determined by genetic influences as well as sensory, cognitive, and affective experiences unique to each individual. This theory maintains that the neuromatrix operates through parallel distributed processing carried out by somatosensory (sensory dimension), limbic (affective dimension), and thalamocortical (evaluative dimension) modules that produce distinct, but related dimensions, which contribute to a unified pain experience.

The present results support the independence of multiple processing networks and confirm that specific cortical regions, particularly the anterior insula, may integrate the output of these separate networks and serve to process an individual's overall sensory/emotional experience. The term interoception has been used to describe an afferent neural system that is representative of "the material me" that may underlie feelings, emotions, and self-awareness (34). Neural activity in the anterior insula has consistently been observed in studies of pain processing (12,46,47). When lesions of the insular region are present, the affective dimension of pain is altered, whereas the sensory-discriminative dimension is spared; this encompasses a disconnection syndrome called asymbolia for pain (13). Altered neural activity in the insula has not been reported in neuroimaging studies of patients with depression, but it has been observed consistently in emotional tasks with negative affective components, such as tasting salt (48) and viewing faces of disgust (49). This func-

tional characterization is consistent with insular projections to the anterior cingulate and amygdalae, and also consistent with the finding that these regions were associated with clinical pain in the present study (50).

This study identified the mediating processes between symptoms of depression or MDD and pain, and their anatomic correlates in the brain. The design could not determine the independent influence of either chronic pain or depression on each other. The ideal way to address the causality between chronic pain and depression in future studies is to evaluate patients with chronic pain as they transition between depressed and nondepressed states. The few existing longitudinal studies suggest that there is, at best, only a weak relationship between improvement in MDD and improvement in chronic pain, and that this relationship diminishes once the influence of other disease-related variables are controlled (51,52). Any preliminary findings on this topic need replication and extension. In addition, in future studies it may be preferable to utilize a longitudinal, within-subject design to examine neural-activation patterns in the same individual over time, as they move from a depressed to a nondepressed state, or vice versa.

Another potentially fruitful series of studies would examine how different types of drug or nondrug therapies impact upon pain processing. For example, previous studies using experimental pain paradigms have suggested that benzodiazepines and opioids may differentially affect sensory or affective-motivational components of pain, but functional imaging has not been used to study similar phenomenon (25).

Finally, it is not clear if the findings of the current study apply only to FM or might be seen more broadly in other chronic pain conditions. It is possible that all chronic pain conditions that have a prominent central element, i.e., characterized by hyperalgesia/allodynia (e.g., irritable bowel syndrome, low back pain, vulvodynia), may show similar features. It is also possible that this phenomenon of neural activation in pain processing might also be noted in more classic peripheral, nociceptive pain conditions such as osteoarthritis or rheumatoid arthritis.

In summary, chronic pain, MDD, and other forms of these conditions frequently coexist. Although it is tempting to lump these constructs together because they can co-occur and may have common mechanisms, it may not be prudent to extrapolate this concept to individual patients. It appears as though there are different and easily distinguished sensory and affective elements to each individual's pain experience. There are strong data suggesting that these elements are somewhat independent of one another and respond differentially to both pharmacologic and nonpharmacologic interventions. Evaluation of these sensory and affective dimensions in patients with chronic pain is likely to improve diagnosis, choice of treatment, and treatment efficacy.

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Using Acupressure to Modify Alertness in the Classroom: A Single-Blinded, Randomized, Cross-Over Trial

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ABSTRACT

Background: Previous reports have suggested that acupressure is effective in reducing pain and improving sleep quality; however, its effects on alertness have not been characterized.

Objectives: The aim of this study was to determine whether two different acupressure treatments have opposing effects on alertness in a full-day classroom setting.

Design: This was a cross-over (two-treatments; three periods), single-blinded, randomized trial.

Setting: The University of Michigan School of Public Health was the setting.

Subjects: Students attending a course in clinical research design and statistical analysis at the University of Michigan participated in the study.

Interventions and outcome measures: Blinded subjects were randomized to two acupressure treatment sequences: stimulation–relaxation–relaxation or relaxation–stimulation–stimulation. Acupressure treatments were self administered over 3 consecutive days. Pre- and post-treatment alertness scores were assessed each day using the Stanford Sleepiness Scale (SSS). Changes in the SSS score (afternoon − morning) were analyzed using a mixed regression model of fixed and random effects. Important factors that were expected to affect alertness, such as caffeine and previous night's sleep, were also assessed.

Results: Baseline characteristics and protocol compliance were similar between the two sequences. Stimulation acupressure treatment yielded a 0.56-point greater difference in score on the SSS, corresponding to less fatigue, compared to the relaxation acupressure treatment ($p = 0.019$). Day of study ($p = 0.004$) and hours of overnight sleep ($p = 0.042$) also significantly affected the change in SSS scores. Incorporating participants' beliefs as to which treatment they received did not significantly alter the observed treatment effect.

Conclusions: Acupressure at stimulation and relaxation points has differential effects on alertness in a classroom setting. Further research is necessary to confirm these findings and to determine whether stimulation and relaxation acupressure are equally effective in influencing alertness.

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INTRODUCTION

Alertness in the workplace has generated considerable attention over the last two decades. Of particular interest is the effect of fatigue in medical trainees, which has recently prompted a significant change in national regulations regarding trainee work hours in the United States.[1] Although studies confirm the negative effects of decreased workplace alertness in a variety of workers, few investigations offer interventions to counteract the effects of fatigue.[2–6]

To date, no reports of acupuncture or acupressure treatments to increase alertness are available. However, these modalities have been evaluated as treatments to improve the quality of sleep and to reduce fatigue. Success rates as high as 90% have been recorded for use of acupuncture in the treatment of insomnia.[7] Tsay et al. examined the effects of acupressure on sleep and fatigue in Taiwanese patients with end-stage renal disease. In one trial, subjects were randomized to acupressure three times per week for 4 weeks, sham acupressure with the same schedule, or control groups without acupressure.[8,9] The acupressure group reported a significant decrease in wake time (amount of time spent awake during "sleeping" hours) as well as an improved score on the Pittsburgh Sleep Quality Index compared to the control group; however, no differences were observed between sham and real acupressure. Similar results were obtained from another study by Tsay assessing changes in fatigue using a visual analog scale.[10] Significant improvements in fatigue were found when comparing the control group to the acupressure and sham acupressure groups, yet no differences were observed between sham and real acupressure treatments. These results suggest that for treating fatigue, sham acupressure may not be an inactive control condition; alternatively, real acupressure may have no significant benefit versus placebo.

Therefore, a single-blind, randomized, cross-over study was conducted to determine whether acupressure has a significant effect on alertness in a population of healthy medical professionals in a prolonged lecture situation. The study used two active treatments, a relaxation treatment and a stimulation treatment, in a cross-over design in which all participants received both treatments on different days. This design avoids the problem of potentially active sham acupressure treatments and maximizes the likelihood of observing an effect of acupressure on alertness, as the two treatments presumably have opposite effects.

MATERIALS AND METHODS

Study objective

The objective of this study was to evaluate the effect of acupressure on the mental alertness of subjects participating in a 3-day lecture environment. The hypothesis was that participants performing stimulatory acupressure would have smaller increases in fatigue from their morning baseline measurements to their end-of-day assessments, compared to days when the same individuals performed a relaxation acupressure technique. The study protocol was reviewed and approved by the University of Michigan Institutional Review Board, and informed consent was obtained from all subjects.

Study population

The study population consisted of 39 subjects enrolled at the University of Michigan School of Public Health course on Clinical Research Design and Statistical Analysis (CRDSA). Inclusion criteria were: (1) $\geq$18 years of age; (2) member of the CRDSA cohort XI; and (3) present during the May 2004 CRDSA session. Exclusion criterion was prior experience with acupuncture or acupressure. Participants included physicians, nurses, dentists, pharmacists, and professionals from the health care industry.

Interventions

Acupressure regimens promoting mental stimulation or relaxation were used in a cross-over design with subjects randomized to either Sequence I (stimulation–relaxation–relaxation) or Sequence II (relaxation–stimulation–stimulation). Each regimen was taught to all study participants by two members of the class who were previously trained in acupressure (one with 3 years and the other with 5 years of experience). The instruction and supervision of acupressure was carried out in separate rooms, on 3 consecutive days during the lunch hour. Each regimen consisted of a 15-minute self-administered session of acupressure at either five stimulatory or five relaxation points (3 minutes each). The stimulatory point formula consisted of Si Shen Chong and bilateral—LI 4, St 36, K 1, and UB 10. These points were chosen based on their ability to reduce fatigue and sleepiness in Traditional Chinese Medical (TCM) theory.[11] The relaxation point formula was selected based on treatment of insomnia in TCM theory and contained Yin Tang and bilateral Anmian, Ht 7, Liv 3, Sp 6.[11] These point formulas were refined by two additional acupuncturists outside of the study but trained in TCM theory (5 years experience each) and the consultation of additional TCM texts by the participating acupuncturists.[12,13] The stimulation and relaxation points are illustrated in Figure 1.

All treatments were performed in cranio-caudal sequence. Acupressure was self administered at Si Shen Chong and Anmian by light tapping with the fingers at a frequency of 2 Hz. All other points were stimulated using either the thumb or forefingers to massage in both clockwise and counterclockwise directions. The style of acupressure administered in this investigation was highly simplified as to allow for the training of participants and to allow for the limited study time period. The instructors demonstrated the intensity of pressure required at each

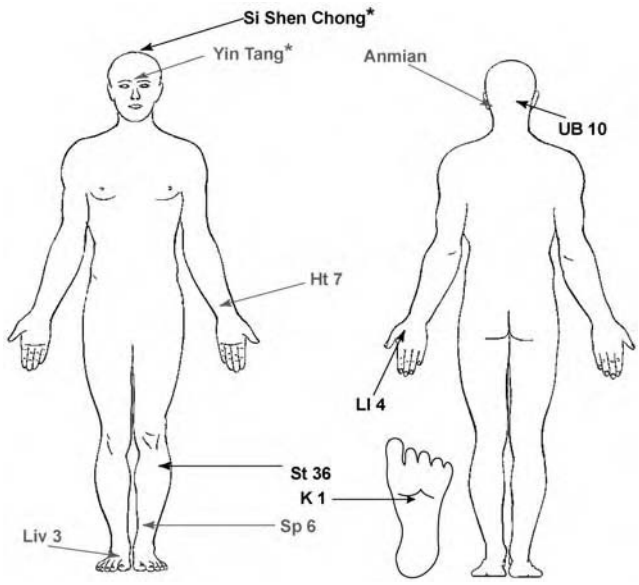

FIG. 1. Body maps of stimulation (**black**) and relaxation (**gray**) acupressure locations. *, Pressure applied unilaterally. All other points were bilaterally stimulated.

point once on all subjects to ensure that adequate pressure was applied.

Randomization

The 39 eligible subjects were randomized to one of two sequences using the pseudo-random number function of a Texas Instruments TI-83 calculator (Dallas, TX). Those in sequence I self administered acupressure in the sequence: stimulation (day 1)–relaxation (day 2)–relaxation (day 3). Those in sequence II self administered acupressure in the sequence: relaxation (day 1)–stimulation (day 2)–stimulation (day 3).

Masking

All subjects were masked as to whether the regimen that they performed each day was the stimulation or the relaxation formula. To assess the success of masking, subjects were asked each day to guess their treatment assignment after administering acupressure. The principal investigators, the randomization team, the data collection team, and the data analysts were also all masked as to the identity of the interventions.

Outcomes

The primary outcome was the difference between afternoon and morning scores on the Stanford Sleepiness Scale (SSS) (afternoon score − morning score).[14] The SSS is an 8-point ordinal scale that assesses subjective sleepiness. The SSS was administered 2 hours before and 3 hours after each acupressure regimen. The 3-hour endpoint was chosen because this was the end of the class period and students were most likely to be fatigued. A daily pretreatment questionnaire included morning sleepiness level as measured by the SSS, hours of sleep the previous night, ounces of caffeinated coffee, ounces of caffeinated tea, ounces of caffeinated cola, alcohol in the last 24 hours (yes/no), and medication use in the last 24 hours (yes/no), the occurrence of any unusual or upsetting events (yes/no), and presence of anxiety that day (yes/no). A compliance and masking questionnaire was also administered each day. The compliance questionnaire contained a Visual Analog Scale asking: "How confident are you that you have self-administered the acupressure treatment appropriately?" with anchors "not confident" and "very confident." After the third and final acupressure period, information was collected about adverse events during the study.

Statistical methods

Data from self-report forms were entered into a Microsoft Access database (Microsoft Corp., Redmond, WA) using a two-person, dictation-entry method. To assess covariate balance by treatment, baseline characteristics were compared between the two treatment sequences. To assess changes over the study period, the same covariates were compared over the 3 study days. Nine subjects with missing data were asked to provide the data retrospectively.

A model was developed using the change in the SSS score from morning to afternoon as the dependent variable, and all other baseline covariates as independent variables. Data were analyzed using the PROC MIXED procedure of SAS version 8.2 (SAS Institute, Cary, NC). This model incorporated the fixed effects of sequence (I or II), period (day 1, 2, or 3), treatment (relaxation or stimulation), and other covariates, as well as the random effects of subject within sequence. Only those variables with values of $p < 0.20$ were retained in the model. A significance level of $\alpha = 0.05$ was used in interpretation of the final analysis. Least-square means of the primary outcome were contrasted for the two treatments.

Masking was evaluated by a 2×2 contingency table analysis of which treatments subjects believed that they had received and their actual treatments. The effect of masking was further evaluated by adding each subject's assessment of the treatment assignment into the model as a covariate.

After inspection of the crude data, one subject from sequence II was identified as an influential outlier. This participant displayed extreme fatigue and sleepiness during the study because of prolonged sleep deprivation from extended travel. As a result this individual's SSS values were abnormally high (ranging from 5 "fighting sleep" to 8 "being asleep"). Becaise this subject was also absent on day 1 and did not receive the relaxation intervention, and because extreme sleepiness may mask any specific effects of acupressure, the final analysis excluded this individual. To investi-

gate the influence of this subject on the study results, an exploratory analysis was performed with inclusion of this outlier.

RESULTS

Between-sequence covariate comparisons

Thirty-nine (39) subjects were randomized into two acupressure treatment arms: 18 to Sequence I (stimulation–relaxation–relaxation) and 21 to Sequence II (relaxation–stimulation–stimulation). There were no differences in gender (I:9 male versus II:12 male; $\chi^2 = 0.199$; $p = 0.656$) or ethnicity (I:14 white versus II:12 white; $\chi^2 = 1.857$; $p = 0.173$) between the two sequences. The distribution of baseline categorical and continuous variables by sequence, treatment, and day are depicted in Table 1. No significant differences were observed for day 1 between treatment groups. Important covariates measured during the study, including compliance, are also presented in Table 1. After treatment on day 1, more subjects in the relaxation acupressure group took naps ($p = 0.048$) and more participants in the stimulation group consumed caffeine ($p = 0.039$). However, there were no differences between the two groups in the quantity of caffeine consumed ($p = 0.317$).

Analysis

A mixed-model regression analysis using the change in SSS as the dependent variable was performed with data excluding the influential outlier. The following variables were retained from the full model: treatment ($p = 0.019$), day ($p = 0.004$), morning caffeine ($p = 0.083$), hours of overnight sleep ($p = 0.042$), and morning upsetting event ($p = 0.071$) (Table 2). No significant carry over effects between days or treatments were detected. The least-square means for the stimulation and relaxation acupressure treatments were 0.570 and 1.127, respectively, with a significant difference in change in alertness scores between the two acupressure treatments.

Table 1. Covariates by Day, Sequence, and Treatment Assignment*

	Day 1			*Day 2*		*Day 3*	
	II	*I*		*I*	*II*	*I*	*II*
	Relaxation	*Stimulation*	p	*Relaxation*	*Stimulation*	*Relaxation*	*Stimulation*
Before acupressure							
Categorical							
AM caffeine	14 (70)	13 (72)	*0.880*	16 (89)	15 (75)	13 (76)	12 (60)
AM upsetting event	10 (50)	11 (61)	*0.492*	8 (44)	4 (20)	3 (17.7)	1 (5)
AM unusual event	3 (15)	3 (16.7)	*1.00*[a]	2 (11)	5 (25)	3 (17.6)	4 (15)
AM nap	0	0	*NA*	0	1 (5)	0	1 (5)
AM alcohol	3 (15)	0 (0)	*0.232*[a]	3 (17)	0 (0)	1 (5.9)	2 (10)
Medication the evening before	9 (45)	4 (22)	*0.140*	6 (33)	7 (35)	6 (35)	7 (35)
Continuous							
AM caffeine (oz)	8.4 (7.3)	12.4 (11.9)	*0.231*	11.3 (8.4)	9.0 (9.0)	10.2 (8.2)	9.7 (13.9)
Hours of sleep the night before	5.4 (1.1)	5.5 (1.5)	*0.821*	5.9 (1.4)	6.0 (1.1)	6.8 (1.4)	6.8 (0.80)
Quality of sleep[b]	2.1 (1.0)	2.2 (1.0)	*0.839*	2.4 (1.1)	2.3 (0.9)	1.8 (0.8)	1.7 (0.8)
After acupressure							
Categorical							
Acupressure interference	1 (5)	1 (5.6)	*1.00*[a]	2 (11)	2 (10)	1 (5.9)	2 (10)
PM nap	5 (25)	0 (0)	*0.048*[a]	1 (5.6)	3 (15)	1 (5.9)	1 (5)
PM caffeine	9 (45)	14 (78)	*0.039*	12 (67)	7 (35)	11 (65)	8 (40)
PM upsetting event	6 (30)	8 (44)	*0.357*	12 (67)	9 (45)	3 (17.7)	1 (5)
PM out of ordinary event	4 (20)	1 (5.6)	*0.344*[a]	6 (33)	5 (25)	1 (5.9)	2 (10)
Continuous							
PM caffeine (oz)	7.6 (10.3)	10.6 (7.2)	*0.317*	7.7 (6.4)	6.1 (9.5)	10.7 (9.1)	6.8 (10.2)
Acupressure minutes	14.8 (0.5)	15 (0)	*0.187*	14.3 (2.4)	14.9 (0.4)	15 (0)	15 (0)
Confident applied well[c]	79.8 (12.9)	71.7 (17.0)	*0.106*	73.9 (20.9)	65.2 (20.6)	76.1 (17.7)	73.7 (17.8)

Categorical variables [count (%)] and continuous [mean (standard deviation)] covariates by day, sequence, and treatment assignment (p values were calculated only for day 1 because treatment effects could affect differences on days 2 and 3.)

*Outlier removed from data.

[a]Fisher's exact test.

[b]Five-point Likert scale (1 = good, 2 = pretty good; 3 = fair; 4 = poor; 5 = bad).

[c]Visual analog scale (0 = not confident; 100 = very confident).

TABLE 2. RESULTS OF MIXED REGRESSION MODELS

		Estimate	*SE*	p-*value*
Final model				
Treatment[a]		0.557	0.232	*0.019*
Day[b]	1	0.753	0.337	*0.029*
	2	−0.256	0.307	*0.407*
	(reference) 3	—	—	—
AM Caffeine (oz)		−0.022	0.012	*0.083*
Hours of sleep night before		0.208	0.100	*0.042*
Pre upsetting event		0.521	0.283	*0.071*
Final model with masking assessed				
Blinding		−0.255	0.245	*0.303*
Treatment		0.483	0.240	*0.048*
Day[c]	1	0.708	0.339	*0.041*
	2	−0.275	0.308	*0.376*
	(reference) 3	—	—	—
AM Caffeine (oz)		−0.022	0.012	*0.077*
Hours of sleep night before		0.205	0.101	*0.046*
Pre upsetting event		0.515	0.284	*0.075*

[a]In this model, if AM caffeine and pre upsetting events are removed, the treatment estimate (SE [standard error]) was 0.523 (0.230) with a *p*-value of 0.0264.
[b]In this model, the *p*-value for the overall fixed effect of day was 0.004.
[c]In this model, the *p*-value for the overall fixed effect of day was 0.006.

The mean difference between morning and afternoon SSS scores are presented by treatment, sequence, and day in Figure 2. The relaxation acupressure treatments consistently produced higher values, corresponding to more fatigue than the stimulation acupressure treatments regardless of sequence or day.

In an exploratory analysis to examine the effect of the outlier's responses on the study results, the above model was fit with data from the outlier included. The significance of treatment ($p = 0.077$), day ($p = 0.015$), hours of overnight sleep ($p = 0.069$), and morning caffeine intake ($p = 0.122$) were changed by this inclusion. In this model, the adjusted least square means for the stimulation and relaxation treatments were 0.736 and 1.196, respectively, with a trend toward less fatigue with stimulation acupressure.

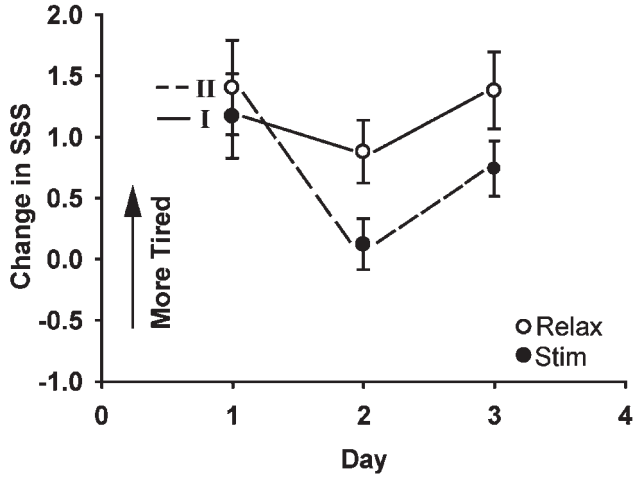

FIG. 2. Plot of mean (standard error) change in Stanford Sleepiness Scale (SSS) (afternoon–morning) scores by sequence and day indicated a significant treatment effect in the final model ($p = 0.0194$). **Solid symbols** indicate stimulation treatment; open symbols, relaxation treatment.

Compliance, masking, and adverse effects

Reported compliance in the study for both acupressure arms was excellent (>90%), and no significant differences between sequences were found.

Masking was assessed by questionnaire after treatment day 1 yielding a continuity-corrected χ^2 test result of $\chi^2 = 2.63$, $p = 0.104$), suggesting that blinding was imperfect. Twenty-five (25) of 38 participants were able to guess their treatment (relaxation or stimulation) correctly on day 1. Over the course of the trial, 62% of participants were able to discern their treatment allocation. To evaluate the significance of the effect of masking on the outcome of the trial, the subjects' assessments of which treatment arm they were assigned were included as covariates in the model with the outlier excluded (Table 2). Although inclusion of masking increased the *p* value from 0.0194 to 0.0484, the treatment effect remained statistically significant in this model as well. The *p* values of the other covariates were slightly changed: day ($p = 0.006$), hours of overnight sleep ($p = 0.046$), morning caffeine intake ($p = 0.077$), and upsetting event in the morning ($p = 0.075$). In this model, the adjusted least square means for the stimulation and relaxation treatments were 0.614 and 1.100, respectively, with significantly less fatigue reported with stimulation acupressure.

Few side-effects were reported. Muscle cramps ($n = 5$), muscle aches ($n = 5$), headaches ($n = 6$), and fatigue ($n = 7$) were the most common side-effects. All were of brief duration and were neither clinically significant for individuals nor statistically significantly different between sequences.

DISCUSSION

This study assessed the effects of two forms of acupressure on the change in alertness in a population of healthy medical professionals in a prolonged lecture situation. It was hypothesized that the two acupressure regimens would differ in their impact on the change in alertness throughout the day after controlling for covariates. This study showed that a stimulation acupressure regimen has a statistically significant reduction in sleepiness, as measured by SSS, compared to a relaxation acupressure treatment. This finding suggests that acupressure can change alertness in individuals who are in classroom settings for a full day.

The use of a cross-over design allowed subjects to serve their own controls, thereby reducing potential confounders. The use of two treatment regimens that had opposing consequences for alertness may have simultaneously increased the magnitude of the treatment effect and removed the problem of noninert sham acupressure treatments present in previous studies.[8–10] The self-administered acupressure treatments were learned easily by the subjects, suggesting that this methodology may be easily disseminated to other subjects with no prior knowledge of acupressure theory or techniques.

However, several limitations were inherent to the study. Although it was a single-blind, randomized design, the majority of study subjects were able to discern their treatment arms, thereby posing a potential bias in the study's primary outcome findings. This problem may have been in part caused by the use of tapping of the Shi Shen Chong site on the top of the head in the stimulation acupressure regimen, which may have been difficult to interpret as relaxing. Despite this weakness, a significant effect of acupressure treatment was still observed when the subjects' assessments of their treatment assignments were incorporated into the model.

A second limitation lies in the potential for generalization of the study findings to the general population. The participants are well educated, are in academic teaching positions, and are active scientific researchers. Moreover, the study was conducted in a clinical trial design class in which the participants were motivated to learn and also compliant. As a result, it remains unclear whether the general population would be as motivated to learn the acupressure techniques or equally compliant with the treatment regimen as was this study population. Furthermore, the results should not be extrapolated to severely sleepy individuals, as evidenced by the effect of including the outlier in our analysis.

A third limitation to the study involves the design of the stimulation and relaxation acupressure arms. Because no accepted stimulation or relaxation acupressure interventions exist, the acupressure sequences used for each treatment were empirically developed. It remains unclear whether these combinations of five points in each acupressure treatment arm are the optimal sites and whether 3 minutes each is the optimal treatment duration. It is quite possible that lesser or greater pressure, duration, or different locations of acupressure may be significantly more effective. In addition, the acupuncture points and formulas implemented here should not be used indiscriminately. Different acupressure techniques used on the same point may have differing outcomes in the hands of trained acupuncturists, a factor not addressed in this investigation.

Although this study showed a statistically significant difference in change in SSS scores between the stimulation and relaxation acupressure arms, it is unclear whether this difference corresponds to a meaningful difference in subject performance using objective outcomes. For instance, it is not clear that a mean difference in change in SSS scores of 0.56 [1.127 (relaxation) − 0.570 (stimulation)] means that stimulatory acupressure will enable students to perform better in classroom settings.

This investigation also raises a potential ethical issue. Participant performance in class may have been compromised by the sedation acupressure. Although the sedating effects of acupressure were not dramatic, future trials may wish to implement a mental alertness task, the results of which would not make a direct impact on the participants.

Finally, because the two treatment arms for comparison were a relaxation arm and a stimulation arm, it is not clear whether stimulation acupressure decreased fatigue, whether relaxation acupressure increased fatigue, or whether both simultaneously occurred. One can only conclude that there was a difference between treatments.

CONCLUSIONS

In summary, this study showed that a stimulation acupressure regimen significantly decreased fatigue and improved alertness in a classroom setting compared to a relaxation acupressure regimen. This significant difference between two acupressure regimens on subjects' perceived fatigue suggests that acupressure may have effects on human alertness. Further studies are required in other populations to determine the scope of this effect, to optimize these acupressure regimens, and to measure performance outcomes to determine whether acupressure has an impact not only on perceived fatigue but also on human function.

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Treatment of Fibromyalgia with Formula Acupuncture: Investigation of Needle Placement, Needle Stimulation, and Treatment Frequency

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ABSTRACT

Objectives: The objective of this study was to investigate whether typical acupuncture methods such as needle placement, needle stimulation, and treatment frequency were important factors in fibromyalgia symptom improvement.

Design/settings/subjects: A single-site, single-blind, randomized trial of 114 participants diagnosed with fibromyalgia for at least 1 year was performed.

Intervention: Participants were randomized to one of four treatment groups: (1) T/S needles placed in traditional sites with manual needle stimulation ($n = 29$): (2) T/0 traditional needle location without stimulation ($n = 30$); (3) N/S needles inserted in nontraditional locations that were not thought to be acupuncture sites, with stimulation ($n = 28$); and (4) N/0 nontraditional needle location without stimulation ($n = 2$ 7). All groups received treatment once weekly, followed by twice weekly, and finally three times weekly, for a total of 18 treatments. Each increase in frequency was separated by a 2-week washout period.

Outcome measures: Pain was assessed by a numerical rating scale, fatigue by the Multi-dimensional Fatigue Inventory, and physical function by the Short Form–36.

Results: Overall pain improvement was noted with 25%–35% of subjects having a clinically significant decrease in pain; however this was not dependent upon "correct" needle stimulation ($t = 1.03$; $p = 0.307$) or location ($t = 0.76$; $p = 0.450$). An overall dose effect of treatment was observed, with three sessions weekly providing more analgesia than sessions once weekly ($t = 2.10$; $p = 0.039$). Among treatment responders, improvements in pain, fatigue, and physical function were highly codependent (all $p \leq 0.002$).

Conclusions: Although needle insertion led to analgesia and improvement in other somatic symptoms, correct needle location and stimulation were not crucial.

INTRODUCTION

Acupuncture has been used as a therapeutic intervention for more than 2500 years in China, and remains an important facet of many modern Asian medical systems.[1] The use of acupuncture as a complementary and alternative form of medicine in Western countries has increased rapidly over the last three decades.[2,3] The U.S. Food and Drug Admin-

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istration (FDA) estimates that Americans spend half a billion dollars per year on acupuncture treatments, most commonly for conditions involving pain,[4] despite the lack of agreement within the scientific community on its efficacy and mechanism of action. Of note, the most appropriate control intervention to use is undecided[5] and it is not clear whether acupuncture efficacy is synergistically dependent on where the needles are placed and whether they are stimulated.[6] As a control some investigators use nontraditional sites,[7–9] whereas others insert needles in traditional acupuncture points but refrain from stimulating them.[10,11]

Fibromyalgia (FM), a condition characterized by chronic diffuse pain, is the second most common rheumatologic disorder, affecting 2%–4% of the populations of industrialized countries.[12,13] To meet American College of Rheumatology criteria for this diagnosis, individuals must have a history of chronic pain in all four quadrants of the body plus the axial skeleton, and have 11 or more (of a possible 18) tender points.[14] Although FM is partly defined by tenderness at these specific anatomic sites, in fact this condition is characterized by generalized tenderness, or hyperalgesia.[15,16] As no universally effective, well-tolerated treatment exists, patients with FM often seek acupuncture.[17] Yet, most studies on the efficacy of acupuncture in FM have been uncontrolled case series,[18,19] and only a single high-quality controlled trial of 70 patients randomized to electro-acupuncture or sham electrical stimulation has provided evidence supporting acupuncture for this condition.[11,20] Although seven of eight outcomes improved in the active treatment group compared to none in the sham group, the extent to which the sham group was blinded was not assessed.

To explore methodological acupuncture issues, a 2×2 factorial was used design to address the following questions: (1) Is acupuncture beneficial for FM? (2) Is the placement of needles in traditional locations, and stimulation of the needles, required for symptom improvement? and (3) Is there a dependence on treatment frequency? It was hypothesized that if needle location and/or stimulation were essential, then an additive or synergistic effect should be detected with traditional or correct needle placement and stimulation. In addition, if acupuncture produces analgesia via a physiologic mechanism, a frequency-dependent improvement in symptoms might be observed.

METHODS

Recruitment

Participants were recruited from the Washington, DC, metropolitan area from August 2000 through January 2002 via announcements in local newspapers and periodicals and were screened on the telephone for study eligibility. Inclusion criteria were: (1) having met ACR criteria for the diagnosis of FM[14] for at least 1 year; (2) reported widespread pain on more than 50% of days; (3) willingness to limit the introduction of new medications or treatment modalities for FM symptoms. Exclusion criteria were: (1) sufficient knowledge of acupuncture techniques to prevent blinding (including previous acupuncture); (2) known bleeding diathesis; (3) autoimmune or inflammatory disease; (4) regular use of narcotic analgesics daily or a history of substance abuse; (5) contraindication to the use of acetaminophen or ibuprophen (rescue analgesics) ; (6) participation in other therapeutic trials; (7) pregnancy or lactation; or (8) receiving disability payments or were involved in litigation related to FM. Subjects were allowed to continue their normal treatment regime(s), including use of antidepressants); however they were asked not to make any additional changes and not to seek acupuncture outside of the trial.

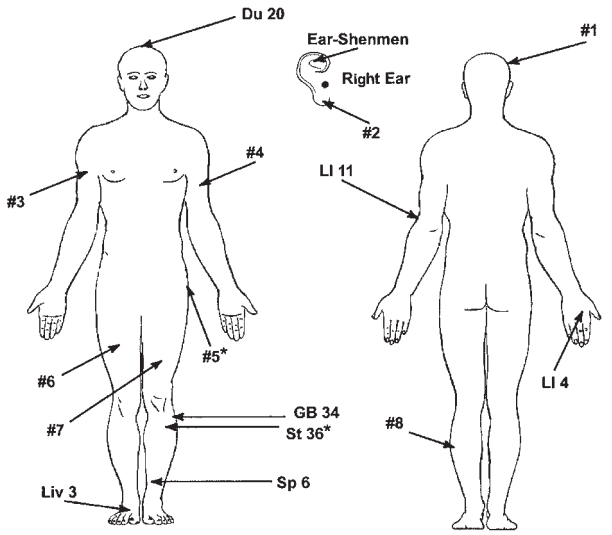
All participants were randomized and allocated to one of four treatment arms using computer-generated random numbers in a four-block design. Treatment allocation was concealed in an opaque envelope and then presented to the acupuncturist 1 day before treatment. All procedures were approved by the local institutional review board; participants received full descriptions of the protocol and gave written informed consent.

Treatment

This study used a 2×2 factorial design to examine the individual and synergistic effects of both needle location and needle stimulation on the efficacy of acupuncture analgesia. The four intervention arms were: (1) T/S (traditional site with stimulation): subjects received acupuncture, at points lying on Traditional Chinese Medicine acupuncture meridians, combined with manual stimulation of the needles; (2) T/0 (traditional site without stimulation): participants received the needles placed at the traditional locations but without any needle manipulation, (3) N/S (nontraditional site with stimulation): participants received the same number of needles placed at the same depths and with the same degree of manual stimulation as the T/S group, but these needles were placed in sites that were not believed to be effective in Traditional Chinese Medicine–based acupuncture; and (4) N/0 (nontraditional site with no stimulation): subjects received needles in nontraditional sites without stimulation. Subjects were told that they would be randomly assigned to one of these treatment groups and would receive either traditional acupuncture therapy or control acupuncture techniques not known to benefit FM. The T/S arm represented traditional Chinese acupuncture whereas the other three arms could be considered as different control groups.

The active point formula (Du 20, LI 11, LI 4, GB 34, bilateral St 36, Sp 6, Liv 3, and Ear-Shenmen)[1] was chosen based on the points' ability to relieve FM symptoms in Traditional Chinese Medicine. Needles placed in the nontraditional groups were not on acupuncture meridians or points (Fig. 1A). The choice of point locations was determined by

A



B

Week	0	1	2	3	4-5	6	7	8	9-10	11	12	13	14-15
Acupuncture sessions per week	0	1	1	1	0	2	2	2	0	3	3	3	0
Outcome Measures:													
Pain (NRS)	X			X	X			X	X			X	X
Fatigue (MFI)	X				X				X				X
Function (SF-36)	X				X				X				X

FIG. 1. Needle locations and temporal outline of study outcomes. **A.** Body maps of approximate needle locations. #, nontraditional points; *, inserted bilaterally. **B.** Representation of study outcomes and acupuncture sessions by week. NRS, numeric rating scale; MFI, Multi-dimensional Fatigue Inventory; SF-36, Short Form–36.

licensed acupuncturists (X.T. and T.X.T., who each have 12 years of experience in treating FM and 17 years of experience with this form of acupuncture).

Treatments followed a forced-titration paradigm: once weekly for 3 weeks, then twice weekly for 3 weeks, and finally 3 times weekly for 3 weeks for a total of 18 sessions. A 2-week wash-out period was inserted between each treatment dose (Fig. 1B). Sterile, 2.54-cm, single-use, disposable, 38-gauge stainless steel needles were used (HBW Supply Inc., Hemet, CA). Stimulation was performed manually by lifting and thrusting while evenly rotating the needle (~12 times at 180 degrees clockwise and counterclockwise). Characteristic *de qi* needling sensations[1] resulting from needle manipulation were elicited in the T/S group but not in the N/S group. There was no intention from the acupuncturist to elicit needle sensations in the N/S group. *De qi* was assessed by the acupuncturist's sensation of needle grasping and by the subject's report to a research assistant. Needles were retained for 20 minutes. More than 95% of the acupuncture sessions were performed by X.T., and the remaining sessions were performed by licensed acupuncturists trained for this study.

Blinding

To ensure and to verify adequate blinding throughout the study multiple measures were taken. Participants from different treatment arms were never present in the acupuncture clinic at the same time. Subjects were asked to refrain from seeking additional information on acupuncture and from discussing acupuncture with other participants, during the time in the study. All subjects were blindfolded during treatment and no verbal communication was allowed between the acupuncturist and the subjects. A nonblinded research assistant was present during all sessions to monitor and ensure treatment integrity. This study was single-blinded. The acupuncturist knew the treatment groups and study hypothesis; however all evaluators of study outcomes were blinded to treatment allocation. Blinding was assessed by questionnaire following the third acupuncture session. This questionnaire read: "What type of procedure do you think you are receiving, acupuncture, placebo (sham), or can't tell."

A priori outcomes

Pain (primary outcome). Subjects completed a 101-point numeric rating scale (NRS) which ranged from 0 to 100 points in 5-point increments. The scale was anchored at 0 by "no pain" and 100 by "worst pain *imaginable*." Clinically meaningful treatment responders were determined using the criteria suggested by Farrar et al.[21]: either a 20-point reduction or a 30% improvement in pain from baseline. On average 85.5% of responders met both criteria, while 9.8% met the 30% improvement criterion only and 4.6% met the 20-point reduction criterion only.

Fatigue. Participants completed the Multi-Dimensional Fatigue Inventory questionnaire[22] and clinically meaningful changes in fatigue were calculated using the Reliability of Change Index (RC).[23] A change of 3.67 in the General Fatigue score from baseline was used to classify fatigue responders. The General Fatigue scores range from 4 to 20 with larger scores indicating more fatigue.

Function. Physical function was assessed with the physical components score calculated from the Short Form-36 questionnaire.[24] This score ranges from 0 to 100 with higher scores indicating better function. Previous work has suggested that a change of seven points in the physical components score is clinically meaningful and therefore we used this value as a cutoff for function responders.

Analysis

A priori it was estimated that a sample size of 30 patients per group was needed to detect 30% differences between

groups with a power of 0.82 and a significance level of 0.05. Longitudinal data were analyzed according to intention to treat. Incomplete data were handled via a last observation carried forward in time. Data were either hand entered or scanned via Teleform (Cardiff Software Inc., Bozeman, MT) and double-checked. Analysis was carried out using SAS (Cary, NC) and SPSS (Chicago, IL) software.

Analyses of variance were performed to determine differences in age, years of disease diagnosis, number of treatments attended, and baseline pain; χ^2 tables were constructed for responder status, male/female ratio, and dropouts. Paired *t*-tests were performed to determine significant changes in NRS pain scores between weeks 3 and 4, 8 and 9, and 13 and 15.

Primary analyses contained two strategies: (1) assessment of changes in mean scores and (2) assessment of changes in binary responder classification. These two approaches were taken to examine the robustness of findings. To examine the effects of location, stimulation, and treatment frequency (dose) on pain, a repeated-measures model was fit to the data by calculating the change in response from baseline to weeks 3, 8, and 13, including fixed effects for a combination of dose, location, and stimulus. Model 1 appeared as follows:

$$y_{ijkl} - x_l = \mu + \alpha_{ijk} + \varepsilon_{ijkl} \quad \text{(Equation 1)}$$

where α_{ijk}, $i = 1, 2, 3$; $j = 1, 2$ and $k = 1, 2$ represents the effect for the i^{th} dose level, j^{th} stimulus, and k^{th} location; x_l is the baseline response for the l^{th} patient. A general correlation structure was assumed across the dose levels to account for within-patient variability across time, as time and dose were confounded in the experiment.

To analyze data from the binary pain outcome (responders versus nonresponders), a similar repeated-measures model was used (model 2). This model used a binomial assumption for the distribution and a logit link leading to a generalized linear model (GLM), as follows:

$$\text{logit } p_{ijk} = \mu + \alpha_{ijk} \quad \text{(Equation 2)}$$

where p_{ijk} represents the probability of responding. The other terms have the same interpretation as model 1. Here, a response value of 1 indicates a 20-point or 30% change on the NRS pain scale of the current pain rating compared to baseline.

RESULTS

Baseline demographics and dropouts

Subject demographics are displayed in Table 1. There were no significant group differences in duration of fibromyalgia ($F = 0.070$; $p = 0.976$) or age ($F = 2.186$; $p = 0.094$). Not unexpectedly, the majority of subjects were female (106/114); however the ratio of female to male subjects was not significantly different across groups ($\chi^2 = 5.019$, $p = 0.136$). No differences were detected in pain scores between groups ($F = 0.215$; $p = 0.886$).

Figure 2 depicts the flow of participants through the study. Thirty-three percent (33%; 38/114) of subjects dropped out of the study before completion. The majority of dropouts occurred in the first 4 weeks (21/38; 55%); the primary reason for dropping out was the time commitment (11/38). There were no significant group differences in dropout rates ($\chi^2 = 3.039$, $p = 0.386$), and the total number of treatment sessions attended did not vary by group ($F = 0.122$; $p = 0.947$; Table 1).

Blinding assessment

To assess whether subjects could determine to which treatment arm they had been randomized, they were asked in week 4, if they thought they were receiving either (a) acupuncture or (b) placebo or (c) could not tell. A χ^2 analysis revealed no significant differences (Fisher's exact $\chi^2 = 7.531$, $p = 0.259$), indicating that participants remained blinded to treatment assignment at week 4.

Table 1. Sociodemographic Characteristics of Fibromyalgia (FM) Study Participants and Average Number of Treatments

Parameter	*T/S*	*T/0*	*N/S*	*N/0*	p
n	29	30	28	27	
Age, years*	46.0 (10.1)	44.5 (10.9)	51.3 (10.0)	48.1 (10.9)	0.094
Female	29	27	24	26	0.136
Years of FM diagnosis*	5.50 (3.71)	5.26 (4.83)	5.17 (4.24)	5.77 (4.10)	0.976
Treatments*	15.7 (1.89)	15.6 (1.80)	15.9 (1.37)	15.7 (1.80)	0.947
Ethnicity					
White	25	27	25	23	
African American	2	2	2	4	
Hispanic	0	0	0	0	
Other	2	1	1	0	

T/S, traditional needle locations with manual stimulation; T/0, traditional needle location without manual stimulation; N/S, nontraditional needle location with manual stimulation; N/0, nontraditional needle location without manual stimulation.

*Values are mean (standard deviation) by treatment group.

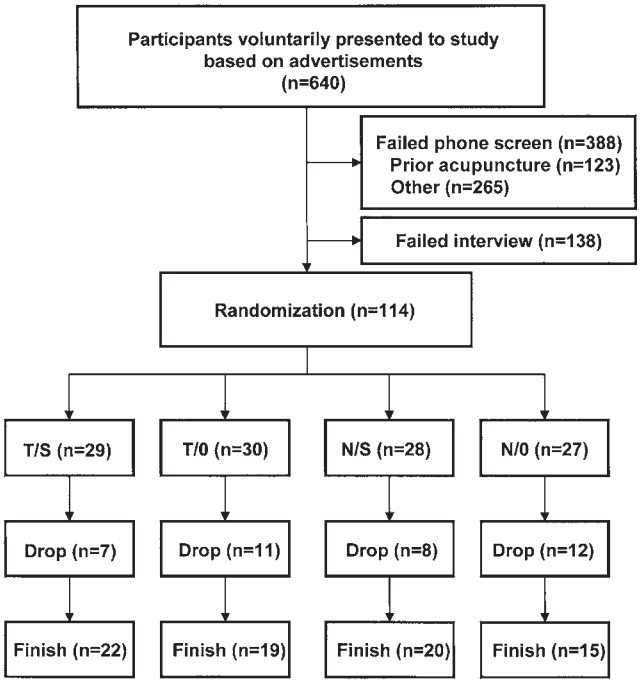


FIG. 2. Flow of participants through study. N/S, nontraditional needle location; T/S, traditional needle location; T/0, traditional needle location without stimulation; N/0, nontraditional needle without manual stimulation.

Needle location and stimulation

Mean pain, fatigue, and function scores are shown in Table 2 and responders are displayed in Table 3. Based on analysis using model 1, no significant effects were obtained for either needle stimulation (weeks 3, 8, 13: $t = 1.03$; $p = 0.307$) or location (weeks 3, 8, 13: $t = 0.76$; $p = 0.450$). Similarly no significant effects were obtained from model 2 for the binary response pain variable for either needle stimulation (weeks 3, 8, 13: $\chi^2 = 3.60$; $p = 0.058$) or location (weeks 3, 8, 13: $\chi^2 = 0.20$; $p = 0.657$).

Figure 3A shows a graphic representation of the percentage of pain responders by time. No group consistently had more improvement than another. Taken together these results suggested that there was no additional benefit derived from placing needles in the correct location, or stimulating the needles, at these time points.

Treatment frequency (cumulative dose)

As exploratory analyses we tested for effects of treatment frequency in data from all four groups combined. A fit of model 1 to the continuous NRS pain scores yielded a significant overall effect for treatment frequency between weeks 4 and 15 ($t = 4.81$; $p = 0.045$) and between weeks 3 and 13 ($t = 4.92$; $p = 0.039$). No significant effects were

TABLE 2. SCORES FOR PAIN, FATIGUE, AND FUNCTION BY ACUPUNCTURE GROUP AND WEEK

	T/S	*T/0*	*N/S*	*N/0*	*Total*
Pain					
Week 0	56.46 (20.46)	53.08 (25.18)	54.57 (24.77)	58.33 (19.70)	55.38 (22.59)
Week 3	54.13 (23.44)	53.27 (23.53)	56.00 (26.29)	54.41 (24.68)	54.36 (23.98)
Week 4	62.95 (22.55)	55.80 (27.07)	60.45 (26.41)	60.29 (25.59)	59.77 (25.15)
Week 8	55.42 (26.82)	46.74 (26.74)	42.86 (28.00)	54.41 (27.61)	49.76 (27.28)
Week 9	48.26 (28.59)	51.92 (27.02)	46.82 (30.69)	60.83 (22.31)	51.52 (27.55)
Week 13	53.26 (32.00)	40.83 (29.92)	44.09 (25.94)	53.82 (23.88)	47.56 (28.52)
Week 15	54.17 (32.09)	53.85 (28.79)	46.30 (25.50)	56.11 (19.14)	52.47 (27.12)
Change[a]	3.20 (26.23)	12.25 (27.55)	10.48 (25.36)	4.51 (21.79)	7.82 (25.56)
p, location[b]	0.450				
p, stimulation[c]	0.307				
Fatigue					
Week 0	16.78 (4.00)	16.33 (3.13)	16.35 (2.95)	17.12 (2.50)	16.60 (3.19)
Week 4	16.35 (3.65)	15.68 (3.46)	16.26 (3.39)	15.78 (3.46)	16.02 (3.44)
Week 9	15.13 (4.01)	15.74 (3.57)	14.73 (3.30)	15.72 (3.08)	15.33 (3.50)
Week 15	15.71 (3.59)	14.59 (4.55)	14.35 (4.20)	15.39 (2.75)	14.98 (3.89)
Change[a]	1.08 (2.95)	1.74 (3.22)	2.00 (3.28)	1.73 (2.95)	1.62 (3.04)
Function					
Week 0	31.80 (7.35)	37.60 (9.22)	37.20 (8.70)	38.13 (6.44)	36.12 (8.42)
Week 4	34.92 (7.87)	39.28 (10.05)	34.84 (8.92)	39.27 (9.57)	37.03 (9.26)
Week 9	35.91 (7.96)	39.91 (9.40)	38.48 (9.85)	40.52 (9.06)	38.66 (9.12)
Week 15	34.73 (8.64)	40.20 (10.47)	38.34 (8.95)	40.52 (10.68)	38.35 (9.80)
Change[a]	−2.89 (7.69)	−2.42 (9.34)	−1.14 (4.79)	−2.35 (7.07)	−2.20 (7.40)

Mean (standard deviation) scores for pain, fatigue and function outcomes by treatment group and week are shown. No treatment group showed significant improvement over the others.

T/S, traditional needle locations with manual stimulation; T/0, traditional needle location without manual stimulation; N/S, nontraditional needle location with manual stimulation; N/0, nontraditional needle location without manual stimulation.

[a]Mean (SD) in change score (pain: week 0–13; fatigue and function: week 0–15).

[b]Model 1, *p* value for comparison of groups: T/S + T/0 vs. N/S + N/0 (weeks 3, 8, and 13).

[c]Model 1, *p* value for comparison of groups: T/S + N/S vs. T/0 + N/0 (weeks 3, 8, and 13).

Table 3. Percentage of Responders by Acupuncture Group and Week

	T/S	*T/0*	*N/S*	*N/0*	*Total*
Pain					
Week 3	8/29 (28)	6/30 (20)	5/28 (18)	6/27 (22)	25/114 (22)
Week 4	3/29 (10)	6/30 (20)	5/28 (18)	5/27 (19)	19/114 (17)
Week 8	6/29 (21)	10/30 (33)	10/28 (36)	6/27 (22)	32/114 (28)
Week 9	8/29 (28)	5/30 (17)	10/28 (36)	4/27 (15)	27/114 (24)
Week 13	8/29 (28)	13/30 (43)	9/28 (32)	7/27 (26)	37/114 (32)
Week 15	9/29 (31)	7/30 (23)	10/28 (36)	6/27 (22)	32/114 (28)
Change[a]	21	3	18	3	11
p, location[b]	0.657				
p, stimulation[c]	0.058				
Fatigue					
Week 4	3/29 (10)	5/30 (17)	3/28 (11)	2/27 (7.4)	13/114 (11)
Week 9	8/29 (28)	4/30 (13)	8/28 (29)	5/27 (19)	25/114 (22)
Week 15	4/29 (14)	6/30 (20)	9/28 (32)	4/27 (15)	23/114 (20)
Change[a]	4	3	21	7.6	9
Function					
Week 4	7/29 (24)	5/30 (17)	1/28 (3.6)	3/27 (11)	16/114 (14)
Week 9	9/29 (31)	7/30 (23)	3/28 (11)	3/27 (11)	22/114 (19)
Week 15	6/29 (21)	8/30 (27)	1/28 (3.6)	4/27 (15)	19/114 (17)
Change[a]	−3	10	0	4	3

Number (percentage) of responders for each outcome by treatment group and week are shown. Clinically significant improvements in pain were observed in 25%–35% of subjects.

T/S, traditional needle location with manual stimulation; T/0, traditional needle location without manual stimulation; N/S, nontraditional needle location with manual stimulation; N/0, nontraditional needle location without manual stimulation.

[a]Percentage of responders changed between first and last assessment week (week 4 to week 15).

[b]Model 2, p value for comparison of groups: T/S + T/0 vs. N/S + N/0 (weeks 3, 8, and 13).

[c]Model 2, p value for comparison of groups: T/S + N/S vs. T/0 + N/0 (weeks 3, 8, and 13).

observed from either once to twice per week or from twice to three times per week (all $p > 0.05$). No dose effect was observed within any of the treatment groups when analyzed separately (all $p > 0.05$) possibly because of the smaller sample size per group compared to the entire cohort.

Figure 3B depicts the overall frequency dependence for NRS pain responders from all four groups combined. A trend of an increasing number of responders was observed and a noticeable decrease in analgesia was detected during the washout periods. This decrease in analgesia was significant from week 3 to 4 ($t = -2.787$; $p = 0.007$) and from weeks 13 and 15 ($t = -2.396$; $p = 0.019$). Together these data suggest that increasing treatment frequency decreased pain and that the cessation of treatment increased pain.

Codependence of outcome domains

To determine whether responder status was independent within the pain, fatigue, and function domains, multiple 2×2 χ^2 tests of treatment responders were performed. Significant codependence in (1) pain–fatigue ($X^2[1] = 15.352$; $p = 0.001$), (2) fatigue–function ($X^2[1] = 10.469$; $p = 0.001$); and (3) pain–function ($X^2[1] = 10.045$; $p = 0.002$) was observed. These data suggest that responder status in all three outcome domains was highly interrelated.

DISCUSSION

Both randomized controlled trials, and longitudinal observation of individuals treated at tertiary care centers suggest that fibromyalgia is difficult to treat.[25,26] As a result, no single intervention is completely accepted by the medical community, and no one intervention has significantly outperformed others.[27,28] The present data provide evidence that a subset of individuals obtained improvements in clinical pain, fatigue, and function from acupuncture, although efficacy was not related to needle placement or stimulation. These results differed from Deluze et al.,[11] which may in part be caused by their use of electro-acupuncture, which is inherently difficult to blind and is a different treatment modality from the manual stimulation used here.

Needle location and stimulation

When performing sham acupuncture, investigators sometimes place needles on nontraditional acupuncture points using a technique termed "minimal acupuncture."[6] However

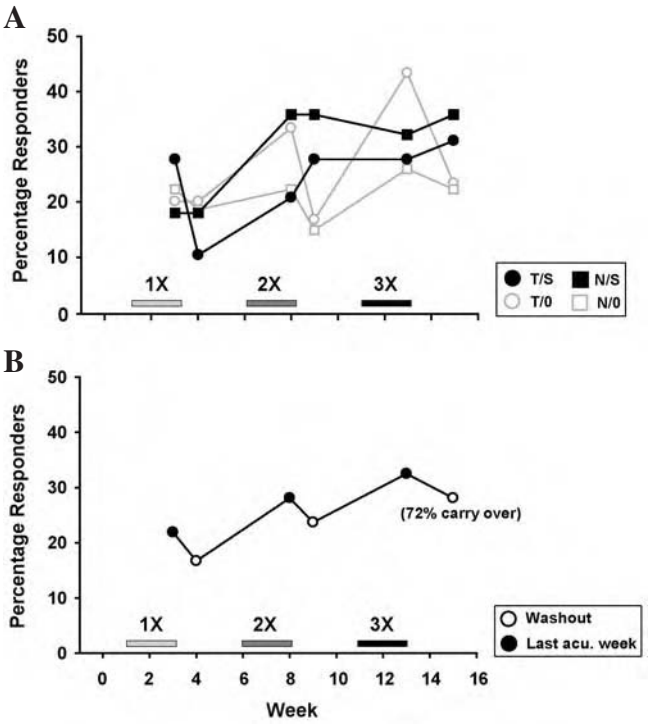


FIG. 3. Effects of needle location, stimulation, treatment frequency, and baseline depressive symptoms on pain responders. **(A)** Plot of percentage of NRS pain responders by group for increasing treatment frequency (1× per week, 2× per week, and 3× per week). No one group consistently displayed more responders than another. **(B)** Plot of percentage NRS pain responders by increasing treatment frequency for all four groups combined. An increasing trend for responders was found. Solid symbols equal final week for each acupuncture dose (weeks 3, 8, and 13) while open symbols are assessment weeks (weeks 4, 9, and 15). Seventy two percent (72%) of responders after 3× per week were also responders after 2× per week. NRS, numeric rating scale. acu., acupuncture.

needle insertion, irrespective of location, may elicit a response that is functionally identical to that in traditional points.[29–33] Indeed, sham needle sites have been shown to be more effective than inert controls,[34] which implies that minimal acupuncture may not be inert. This may have been the case for the nontraditional groups, and perhaps the use of a more inert control intervention[35,36] would clarify this issue.

Acupuncture advocates may suggest that FM is an inappropriate condition for the study of the specifics of needle placement. In Traditional Chinese Medicine, *Ashi* points are commonly used for the treatment of pain originating away from the major meridians, and needles are placed exactly where the pain is located, regardless of whether the pain lies on a meridian or does not correspond to a particular acupuncture point.[1] Because FM pain is diffuse and located throughout the body, our nontraditional locations may have actually functioned as *Ashi* points.

Nonetheless no difference in clinical pain was detected regardless of whether the needles were stimulated. This indicates that the needle manipulation used in this study is not an essential component to acupuncture therapy in FM, and it follows that needle sensations elicited by manual manipulation are not critical in this setting. However it should be noted that some forms of acupuncture use no manual stimulation. The form of acupuncture administered here was highly simplified for experimental purposes; in a real clinical setting, elements such as needle stimulation might enhance the effectiveness of this therapy.

Frequency dependence

A hallmark of effective pharmacologic interventions is the dose–response effect. In theory, interventions that effect changes in physiological substrates should result in dose dependency, in which a greater effect is elicited with an increase in the magnitude of the therapeutic intervention. In exploratory analyses, data were reported supporting this hypothesis for an overall effect of treatment frequency in FM. This effect was modest, as it was only observed when all four treatment groups were combined. With the absence of a no-treatment arm, one cannot exclude regression to the mean, natural history, or other time effects as possible mechanisms for the frequency dependence because time and dose were confounded in this study. However this seems unlikely for two reasons: first, an overall decay in analgesia was observed during the wash-out periods (Fig. 3B), suggesting that treatment was related to pain relief; and second, the natural trend of pain fluctuation in fibromyalgia does not match the magnitudes observed here.[25]

Reduction of pain in fibromyalgia by a "placebo effect" of acupuncture

In light of the fact that no differences were observed for either stimulation or location of the needles within this study, one may be tempted to conclude that the effects of acupuncture occur largely because of a "placebo effect." Indeed the criteria used to designate responders from nonresponders lies well within the range of the placebo effect.[37] The placebo effect may have diluted any specific effects of acupuncture observed in this trial; however further studies will be required to confirm or refute these findings.

CONCLUSIONS

In this controlled trial, a subset of FM subjects received symptom improvement with acupuncture needle insertion, but no specific effects of needle placement or stimulation were noted. Alternative designs containing more "inert" comparison groups or trials with fewer dropout rates may be more helpful in assessing which specific factors are necessary to engender these effects. More specialized treatment regimens tailored to individual FM participants may also yield more positive findings.

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Characterization and Consequences of Pain Variability in Individuals With Fibromyalgia

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Objective. **A growing body of evidence suggests that real-time electronic assessments of pain are preferable to traditional paper-and-pencil measures. We used electronic assessment data derived from a study of patients with fibromyalgia (FM) to examine variability of pain over time and to investigate the implications of pain fluctuation in the context of a clinical trial.**

Methods. **The study group comprised 125 patients with FM who were enrolled in a randomized, placebo-controlled trial of milnacipran. Pain intensity levels were captured in real time by participants using electronic diaries. Variability in pain was assessed as the standard deviation of pain entries over time (pain variability index [PVI]).**

Results. **Substantial between-subject differences in pain variability were observed (mean ± SD PVI 1.61 ± 0.656 [range 0.27–4.05]). The fluctuation in pain report was constant over time within individuals ($r = 0.664$, $P < 0.001$). Individuals with greater variability were more likely to be classified as responders in a drug trial (odds ratio 6.14, $P = 0.006$); however, this association was primarily attributable to a greater change in pain scores in individuals receiving placebo ($r = 0.460$, $P = 0.02$) rather than active drug ($r = 0.09$, $P > 0.10$).**

Conclusion. **Among individuals with FM, there were large between-subject differences in real-time pain reports. Pain variability was relatively constant over time within individuals. Perhaps the most important finding is that individuals with larger pain fluctuations were more likely to respond to placebo. It is not clear whether these findings are applicable only to patients with FM or whether they may also be seen in patients with other chronic pain conditions.**

Clinical practice as well as research data indicate that the intensity of chronic pain typically is not constant (1–3). This phenomenon may be particularly true in patients with fibromyalgia (FM) (4,5). FM is defined by the presence of widespread pain and tenderness (6) and affects 2–4% of the population (7). Within a single day, an individual with FM may note that his or her level of pain varies greatly; it is not uncommon for pain scores on a 10-cm visual analog scale (VAS) to range from 2 to 10 (5). This variability in pain magnitude reflects a volatility of pain in some individuals, yet relatively few studies have examined this characteristic.

Variation in the intensity of chronic pain has been thought to arise from the following 2 sources: systematic trends in pain levels that may be attributable to the pathogenesis of the condition (1–3), or fluctuations about a mean pain level that lack any underlying trend (1). Although some investigators have suggested that individuals with less predictable pain (i.e., no trend) have more depressive symptoms (2), this has not been confirmed by others (3).

The lack of studies focusing on pain variability within individuals over time may be due, in part, to the limits of previous data-recording methods, such as pencil-and-paper diaries (8). These problems have been largely overcome by the use of electronic diaries that capture symptoms in real time, using high sampling densities (9). We examined the within-subject pain variability across time in individuals with FM who were

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Dr. Hufford has received consulting fees or honoraria (more than $10,000 per year) from Invivodata and owns stock in Invivodata.

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enrolled in a clinical trial in which electronic diary methods were used.

The main questions of interest were as follows: What is the within- and between-subject variability of FM pain over time? How does pain variability differ across subjects? Finally, is there any information about an individual's pain variability that may be helpful in designing clinical trials in FM?

PATIENTS AND METHODS

Phase II drug trial of milnacipran in FM. The study group comprised 125 patients with FM who were enrolled in a multicenter drug trial of milnacipran (a dual serotonin/norepinephrine reuptake inhibitor) versus placebo (10). Briefly, participants were randomized to receive either milnacipran or placebo after a 2-week baseline (observational) period and were followed up longitudinally for 12 weeks.

Patients with FM who were 18–75 years of age and met the American College of Rheumatology 1990 criteria for FM (11) were included in the study. Key exclusion criteria included severe psychiatric illness (although individuals with major depression or generalized anxiety disorder were not excluded); risk of suicide according to the investigator's judgment; alcohol or drug abuse; history of significant cardiovascular, respiratory, endocrine, genitourinary, liver, or kidney disease; systemic infection; cancer or current chemotherapy; significant sleep apnea; life expectancy of <1 year; and active peptic ulcer or inflammatory bowel disease. All participants gave informed consent, and the protocol was approved by the relevant institutional review boards.

Outcomes. Each participant carried a Palm-based electronic diary (invivodata, Pittsburgh, PA) and was prompted at random intervals (a mean of 3.4 times per day) to enter his or her pain level, using an anchored logarithmic scale (the Gracely Box Scale [GBS]; range 0–132) (12). These values were scaled down by a factor of 6.6 to facilitate comparison with the original GBS (range 0–20).

Statistical analysis. *Calculation of the pain variability index (PVI).* For each participant, the standard deviation of sequential entries within 2-week time blocks was used as the primary measure of the variability or spread in the data (PVI). This outcome was chosen because of its ability to capture both systematic and nonsystematic fluctuations in pain. In addition, this approach makes fewer assumptions about the structure of the data, such as averaging pain levels across or within days. The PVI was calculated separately for each individual and was then used to create a histogram representing all study participants. Mean pain levels were also calculated as the average of all entries over 2-week time blocks.

Distribution properties of the PVI. To test for ceiling or floor effects, the population was divided into quartiles based on individual PVI scores obtained during the first 2 (baseline) weeks. Histograms of the mean pain scores for the upper (highly variable) and lower (less variable) PVI quartiles were compared for skewness.

Stability of the PVI over time. To examine the stability of the measure, individual PVI scores during the 2 baseline weeks and the final 2 weeks of the trial (12 weeks later) were compared using a bivariate Pearson's correlation.

Relationship of the PVI to treatment responsiveness. To determine the relationship between pain variability and responsiveness to treatment (milnacipran or placebo), 3 analyses were performed: logistic regression, linear regression, and univariate correlations. For the logistic regression analysis, the binary response criterion (4-unit change in GBS from baseline to the end of treatment, which represents an ~50% improvement in pain [13]) measured with the electronic diary was used as the dependent variable. This criterion was chosen because it is within the range to designate clinical pain responders (13) and is used here to designate treatment responders. Treatment assignment (milnacipran or placebo) and ln(PVI) were entered as predictors. Age, duration of FM, and race (white = 1, nonwhite = 0) were also added as additional covariates. Goodness of fit was assessed with the Hosmer–Lemeshow test. For the linear regression analysis, the above covariates, in addition to the mean level of pain at baseline, were used to predict change in the mean level of pain (baseline − end).

For the univariate analysis, correlations were made between ln(PVI) and the change in the mean electronic diary pain scores (baseline − end) for individuals receiving placebo or milnacipran. PVI data were transformed to the log of PVI to better approximate the normal distribution needed to meet the assumption of the statistical methods being used. Graphs of random prompt entries of pain versus time were made for all milnacipran responders, to examine the time course of drug application on real-time pain assessment. A *t*-test was performed to detect differences in baseline PVI scores between individuals in whom either an exponential or a linear trend in pain was observed.

Analyses were performed using SPSS version 12.0.1 (SPSS, Chicago, IL) and SAS version 8.02 (SAS Institute, Cary, NC) software.

RESULTS

Demographics. The study population (n = 125) comprised predominantly middle-age (mean ± SD age 47.05 ± 11.15 years) women (n = 122), which is consistent with the epidemiology of FM (14,15). Most of the subjects (n = 105) were white (12 were Hispanic, 5 were African American, 1 was Asian, and 2 were of other ethnicity), and most reported high levels of pain (mean ± SD pain score 6.90 ± 1.78) (on a 10-cm VAS) at baseline. The mean ± SD duration of FM was 4.06 ± 4.16 years.

Characteristics of the PVI. *Within- and between-subject variation in the PVI*. To examine the degree of variability in pain across all participants, a between-subject histogram of PVI values was created for data collected during the 2-week baseline period (Figure 1A). This distribution had a single mode and was skewed toward higher values (mean ± SD PVI 1.61 ± 0.656; $P = 0.002$). A logarithmic transformation provided a good

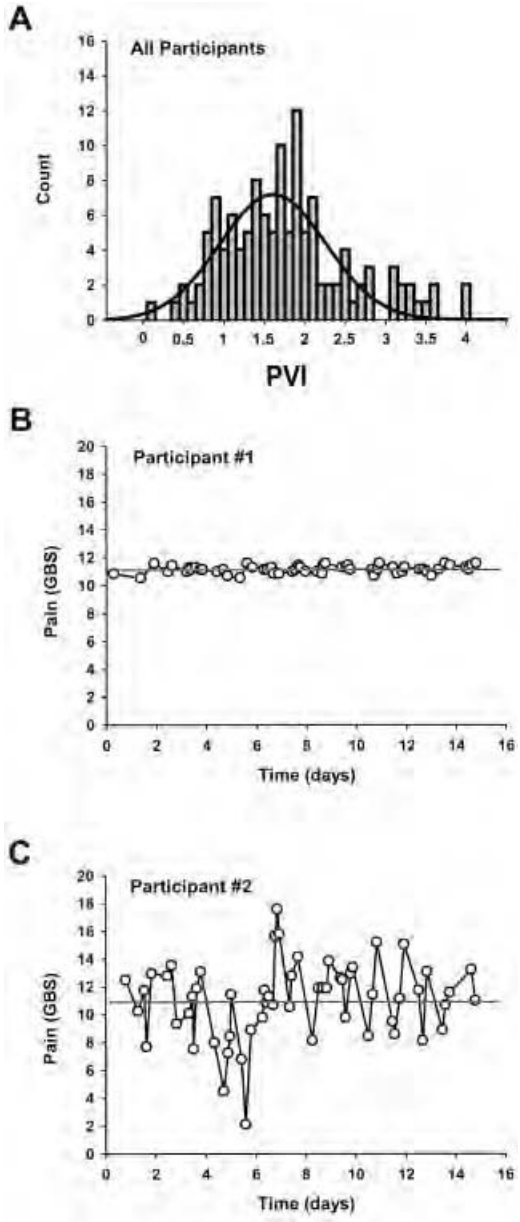

Figure 1. Pain variability in patients with fibromyalgia. **A,** Histogram of pain variability index (PVI) scores for all individuals, showing a single peak with a relatively large spread. **B** and **C,** Consecutive entries of pain levels for participant 1 and participant 2, respectively. Participant 1 displayed relatively consistent levels of pain over time, whereas participant 2 displayed greater variability. Horizontal lines show the mean. GBS = Gracely Box Scale.

fit to a normal distribution for PVI ($P = 0.20$). A large spread in the PVI was observed between subjects (PVI range 0.27–4.05), indicating significant variation in real-time measurements of pain across participants.

Figures 1B and C depict the raw pain scores for 2 different participants tracked longitudinally over 14 baseline days. Although these 2 individuals had similar mean pain scores (11.14 for participant 1 and 11.03 for participant 2), their pain score variability was noticeably different (for participant 1, PVI = 0.27; for participant 2, PVI = 2.78).

Ceiling or floor effects. To test for ceiling or floor effects, mean pain score distributions for the upper (more variable) and lower (less variable) PVI quartiles were investigated for asymmetries. Similar pain scores would be predicted if ceiling or floor effects were absent. The skewness and range in pain scores were relatively similar between quartiles (skewness [SEM] for the lower quartile 0.26 [0.42], for the upper quartile 0.30 [0.42]; range for the lower quartile 9.25–17.49, for the upper quartile 5.33–16.57), suggesting that ceiling and/or floor effects were not largely responsible for the between-subject variability in the PVI.

Trait variability. To assess whether symptom variability may represent a trait, we examined the correlation of the PVI observed at 2 different time periods (baseline versus 12 weeks later). The PVI within individuals was highly correlated over time ($r = 0.664$, $P < 0.001$), suggesting that this is a relatively stable construct.

Effects of PVI in a drug trial. *Association of PVI with response to placebo*. We next investigated the extent that pain variability (PVI) influenced binary responder classification as assessed by electronic diary methods in a drug trial. A logistic regression on responder status was performed using age, race, duration of FM, treatment (milnacipran versus placebo), and ln(PVI) as predictors (Table 1). Treatment, ln(PVI), race, and duration of FM significantly predicted response. Interestingly, individuals with increased pain variability were more likely to be responders. This finding was replicated in a linear regression analysis using the change in pain (mean at

Table 1. Results of logistic regression analysis of clinical pain responder status*

Predictor	Estimate	SEM	OR	*P*
ln(PVI)	1.815	0.660	6.143	0.006
Duration of FM, years	0.145	0.062	1.156	0.020
Race (white vs. nonwhite)	−1.462	0.643	0.232	0.023
Treatment (milnacipran or placebo)	1.706	0.759	5.507	0.025
Age	0.019	0.023	1.019	0.405

* Each independent variable was force-entered into the following regression model: logit(responder: 0,1) = ln(pain variability index [PVI]) + duration + race + treatment + age. OR = odds ratio; FM = fibromyalgia.

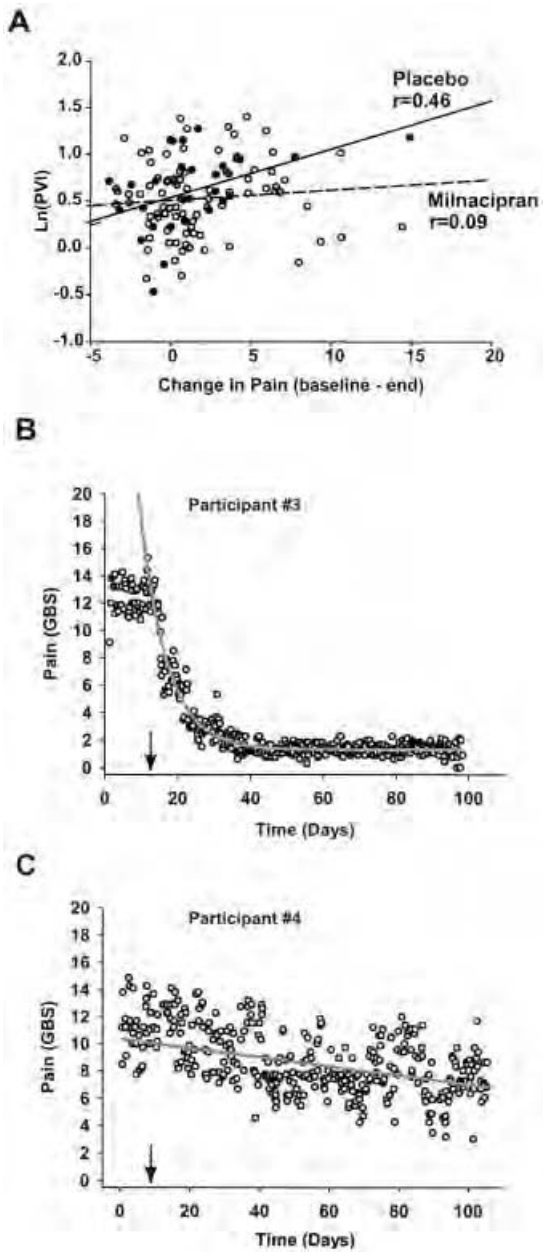

Figure 2. Relationship between the pain variability index (PVI) and the response to placebo. **A,** Scatterplot showing the change in mean pain scores (baseline − end) versus ln(PVI) for individuals receiving placebo or milnacipran. A significant correlation was observed for those receiving placebo (r = 0.460, $P = 0.02$) but not for individuals assigned to milnacipran (r = 0.09, $P > 0.10$). **B** and **C,** Consecutive diary entries for 2 typical individuals. The plots for participant 3 (**B**) and participant 4 (**C**) showed differing courses following administration of milnacipran (arrows). Participant 3 displayed an exponential decline in pain ($\tau = 7.30$ days), whereas participant 4 displayed a linear trend (slope = −0.034/day). Note that participant 4 had increased variability in pain reporting over the course of the trial, as compared with participant 3.

baseline − mean at end) as the dependent variable. A significant effect of ln(PVI) on change in pain ($\beta = 1.624$, $P = 0.028$) was observed after adjusting for age, duration of FM, race, and baseline pain levels, again with greater PVI predicting larger improvements in pain. This association was primarily attributable to greater changes in pain scores in individuals receiving placebo. Figure 2A depicts the association between ln(PVI) and the change in mean pain scores within the 2 study arms. Variability was significantly correlated with a change in pain for those randomized to placebo (r = 0.460, $P = 0.02$) but not for patients receiving milnacipran (r = 0.09, $P > 0.10$).

Association of PVI with nonspecific response to drug. Because treatment response was associated with the PVI among placebo responders, we investigated placebo or nonspecific response patterns in the real-time pain entries for responders receiving milnacipran (n = 33), over the entire study period. Two major types of profiles were observed: an exponential decline in pain, or a linear trend toward reduced pain. Figure 2B shows the pattern for participant 3, who displayed an exponential decline in pain, and Figure 2C shows the pattern for participant 4, who displayed a linear trend. Of the 33 responders given milnacipran, 13 displayed an exponential pattern, 15 displayed a linear pattern, and 5 had other patterns of pain. Those displaying a linear decline in pain had significantly greater baseline pain variability than those displaying an exponential decline in pain (mean ± SD ln[PVI] 0.73 ± 0.31 linear, 0.47 ± 0.35 exponential; $P = 0.048$).

DISCUSSION

In this study, we explored pain variability in patients with chronic FM who were participating in a drug trial. Our results confirm previous findings (5) that temporal fluctuations in FM pain span a continuum, with some individuals displaying a large variation in pain intensity while others have more constant levels.

Pain variability was moderately stable over time. Individuals in whom pain was classified as highly variable at one time point tended to be classified as having highly variable pain patterns later. In addition, variability in pain was not explained by data-collection artifacts such as ceiling or floor effects, because pain score distributions were similar in participants with a large versus a small PVI. One would expect these distributions to have differing skewness if floor or ceiling effects were present. Instead, pain variation was attributable primarily to fluctuations around a stable mean score.

One advantage of this investigation is that we were able to assess the consequences of pain variability in a drug trial. We observed that pain variability predicts drug responsiveness. Individuals with a greater PVI at baseline were more likely to be responders; this effect was seen almost exclusively in those randomized to placebo as compared with those receiving milnacipran, suggesting that high pain variability may be a predictor of a placebo response.

If this is correct, one would also predict that this effect would also be present to some extent within responders to milnacipran, because placebo mechanisms should also occur in those randomized to active drug. Interestingly, our real-time pain data demonstrated that some milnacipran responders displayed a nonspecific response to drug (i.e., a gradual linear decline in pain during milnacipran therapy). Individuals with such a nonspecific response also had greater baseline pain variability than those displaying a more immediate (i.e., exponential) response.

These results have direct implications for drug trials in FM and perhaps broader implications for other pain syndromes. Although we detected no difference in PVI scores between the 2 study arms in our trial ($P > 0.05$), investigations that randomize individuals with greater baseline PVI scores to placebo may be biased toward the null due to a greater placebo effect. To counteract or control for this effect, one could either stratify participants based on baseline PVI scores or even remove individuals with high pain variability prior to randomization. Examining the pattern of response to placebo interventions may also offer further insight into the mechanisms of placebo-induced analgesia.

This investigation has several limitations. First, our results may be limited to patients with FM. Second, participants were enrolled in a drug trial, and the stability of their pain may have been influenced by treatment. Third, most participants were women, and as such our results may not be applicable to a male population, especially because it is known that women display changes in pain intensity depending on the time of their menstrual cycle (16). Fourth, we did not make an attempt to differentiate systematic versus nonsystematic trends in the data when estimating variability. Finally, most of our participants were white, thus limiting the applicability of our conclusions to this population.

In some patients with FM, the variation in pain intensity over time is significant. This variability is relatively constant within individuals and may predict a nonspecific response to treatment (i.e., a placebo effect). Extrapolation of these results to other chronic pain states is warranted.

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Psychophysical Outcomes From a Randomized Pilot Study of Manual, Electro, and Sham Acupuncture Treatment on Experimentally Induced Thermal Pain

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Abstract: **In this pilot study comparing the analgesic effects of three acupuncture modes—manual, electro, and placebo (with Streitberger placebo needles)—in a cohort of healthy subjects, we found that verum acupuncture treatment, but not placebo, lowered pain ratings in response to calibrated noxious thermal stimuli. This finding was mainly the result of highly significant analgesia in 5 of the 11 subjects who completed the 5-session study. Of the 5 responders, 2 responded only to electroacupuncture and 3 only to manual acupuncture, suggesting that acupuncture's analgesic effects on experimental pain may be dependent on both subject and mode. We developed a simple quantitative assessment tool, the Subjective Acupuncture Sensation Scale (SASS), comprised of 9 descriptors and an anxiety measure to study the relationship between the *deqi* sensation induced by acupuncture and the putative therapeutic effects of acupuncture. The SASS results confirm that the *deqi* sensation is complex, with all subjects rating multiple descriptors during each mode. We found significant correlations of analgesia with SASS ratings of numbness and soreness, but not with ratings of stabbing, throbbing, tingling, burning, heaviness, fullness, or aching. This suggests that attributes of the *deqi* sensation may be useful clinical indicators of effective treatment.**

Perspective: ***The results of this study indicate the existence of both individual subject and acupuncture mode variability in the analgesic effects of acupuncture. This suggests that switching acupuncture mode may be a treatment option for unresponsive patients.***

Key words: *Acupuncture, acupuncture analgesia, acupuncture mode, deqi sensation, pain.*

For more than 2000 years, acupuncture has been widely used in many cultures to relieve pain. Rigorous studies documenting the efficacy of acupuncture in reducing clinical pain is limited, with good evidence only for dental pain[7] and inconclusive or equivocal evidence for other pain disorders.[3,8,9,15,16,22,26,34] Basic science research investigating the salubrious effects of acupuncture treatment has produced results that have led to specific testable mechanistic hypotheses (eg, postulating roles for endogenous opioids[13,14,25]); however, these have not been related directly to reputed clinical analgesic effects. Methodologic challenges that confound clinical trials of acupuncture analgesia are numerous and have been difficult to overcome.[17-19,40] Development of robust sham acupuncture methods is a critical step toward evaluating efficacy and potential therapeutic mechanisms.

Although acupuncturists traditionally have used manual needle manipulation to achieve therapeutic benefits, electro acupuncture is gaining popularity in clinical practice. Previous studies in healthy subjects suggest that different mechanisms may be involved in manual and electro acupuncture treatments.[6,21,39,41,42] Although treatment with both manual and electro acupuncture modalities has reduced subjective ratings of experimental pain,[4,13,24,25] none of these studies compared their analgesic efficacy in a single subject cohort. In addition, the response to acupuncture is believed to be a trait characteristic (ie, individuals can be good or poor responders), yet there is little evidence comparing the response to different acupuncture modalities within individuals.

The evocation of *deqi,* a sensation of numbness and fullness that develops at the site of stimulation, is believed to be important for acupuncture analgesia.[1,31]

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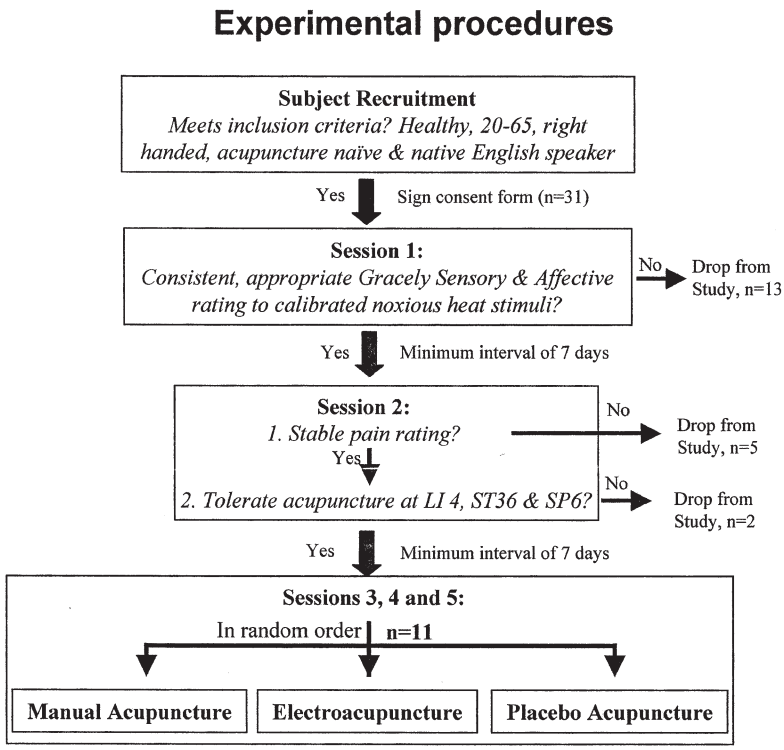

Figure 1. Flow chart of experiment.

Traditionally, patients are asked to remain aware of the sensation during treatment. Scientific evidence of the importance of the *deqi* sensation for treatment outcomes is limited, but one trial showed that *deqi* was the predictor of a positive outcome in osteoarthritis.[32] Thus, *deqi* may be an important variable in studies of the efficacy and mechanism of the action of acupuncture treatment.[37] However, there is no consensus for a method or instrument to quantify the *deqi* sensation despite efforts toward this goal.[27,37,40] Particularly, no studies to our knowledge have systemically investigated the relationship between different aspects of *deqi* and any treatment effects.

We hypothesized that individuals may respond differently to manual, electro, and placebo acupuncture and designed a study to investigate the influence of the two verum modes of acupuncture and placebo acupuncture on the psychophysical responses to noxious thermal stimuli in healthy subjects. We also administered an assessment tool to collect measures of subjective acupuncture-induced sensations to determine association of *deqi* traits with therapeutic effects.

Material and Methods

Subjects

Thirty-one right-handed subjects (23 males, mean age 25.1 ± 3.5 [SD] years) who were naive to acupuncture participated in the study. All subjects were recruited by advertisement. A telephone screening was carried out to exclude subjects with medical disorders, including neurologic and psychologic disorders. Experiments were conducted with the understanding and written consent of each subject and approval by the Human Subjects Committee at Massachusetts General Hospital.

Procedures for the Delivery and Assessment of Noxious Thermal Stimuli

Thermal stimuli were delivered by a TSA-2001 thermal sensory analyzer with a 3 × 3–cm probe (Medoc Advanced Medical Systems, Rimat Yishai, Israel) running a proprietary computerized visual analog scale software (COVAS). Heat stimuli were 12 seconds in duration (including the ~3.5-second ramp up and down from baseline, the temperature ranged from 41°C to 52°C) with a minimum interstimulus interval of 20 seconds. The probe was moved between each stimulus application by a research assistant. Each stimulus was separated by a minimum distance of 4 cm to minimize sensitization of the skin. Sequences of stimuli were applied on alternating sides and limbs. To ensure that stimuli were consistently applied, nonoverlapping sensory fields were labeled by grids drawn on the volar aspect of the forearms between the creases of the wrist and elbow and the medial aspect of the shins between the ankles and the knees in each session.

Each subject was studied in 5 sessions (Figure 1); the first 2 sessions were training sessions, and the 3 subsequent sessions were experimental sessions. Sessions were separated by at least 1 week to avoid sensitization to repeated application of the noxious stimuli and to allow for full recovery of the subject's skin. Subjects were asked

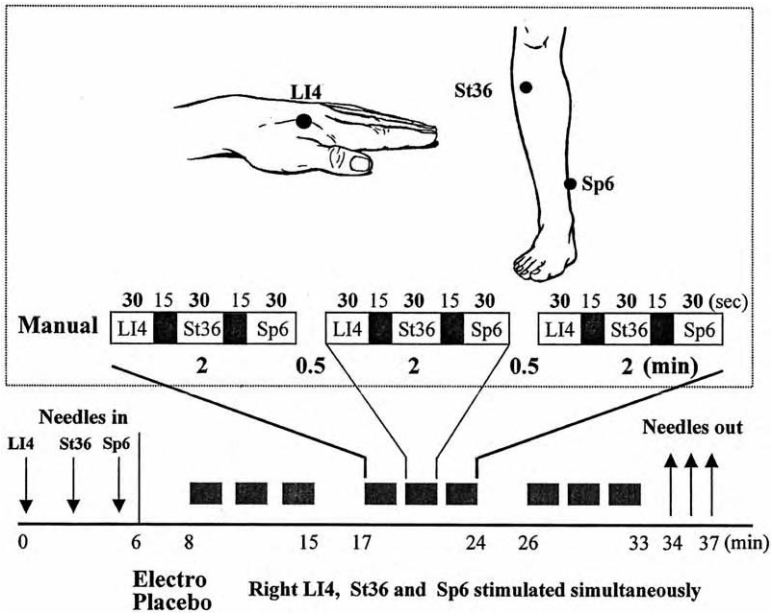

Figure 2. Schematic diagram of the acupuncture treatment procedures.

to hold common daily activities constant on experiment days (ie, duration of sleep, eating habits, caffeine intake). They also were asked not to shave their legs on the 2 days before a session.

In the first training sessions, subjects were trained to use Gracely Box 0-20 categorical scales with anchor words[11,12] to orally rate the sensation elicited by each pain stimulus. Three discrete temperatures were selected for each subject so that the subject consistently reported ratings in a target LOW, MEDIUM, and HIGH range (7-10, 11-14, and 15-18, respectively, on the Gracely Sensory Box Scale). Then, exactly the same 4 sequences of stimuli that were used during the rest of the sessions were administered. Thermal sequences consisted of 9 stimuli, 3 each of LOW, MEDIUM, and HIGH intensities administered in random order with different temperatures for arms and legs within the same individual. In the second training session, only these sequences were presented to establish the reliability of the subject's responses across sessions. At the end of Session 2, acupuncture was administered for 5 minutes. Subjects were then familiarized with our acupuncture sensation rating instrument (see below for further details) for both manual and electro acupuncture stimulation at each acupoint.

Screening criteria based on performance of the sensory rating task had to be met for a subject to proceed to the 3 experimental sessions. First, in the initial training session, subjects had to report subjective ratings that showed a clear correlation to the magnitude of the stimulus intensity during the administration of the stimuli on all 4 limbs. Second, subjects were required to report subjective ratings to their LOW, MEDIUM, and HIGH intensity noxious stimuli between the 2 training sessions that were within 15% as determined by the mean sensory scores. Only subjects who passed all screening criteria continued to the 3 experimental sessions.

The experimental sessions (Sessions 3-5) were identical for all subjects except for the acupuncture mode administered, the order of which was randomly assigned across subjects. Noxious thermal stimuli were presented approximately 5 minutes before and after administration of 1 of 3 modes of acupuncture (electro, manual, or placebo) by the same licensed acupuncturist. An identical series of 9 noxious stimuli in random order was applied to each limb with the order of right leg, left arm, left leg, and right arm before and after treatment.

To maintain uniform expectancy across treatments, subjects were told that they would receive 3 modalities of acupuncture, one in each of the 3 sessions, to investigate the efficacy of acupuncture analgesia. They were also told that the 3 modalities of acupuncture stimulation may produce distinct sensations and may work through different mechanisms, and the efficacy of one mode of acupuncture may not be associated with the efficacy of the other modes. At the end of Session 5, subjects were debriefed and asked to comment on their general experience of the pain stimuli, acupuncture modes, and testing conditions. They were also specifically asked if they thought any of the treatments had been a placebo.

Procedures for Acupuncture Administration

Three acupoints on the right side of the body were used in this study. They were Large Intestine 4 (LI4), Stomach 36 (St36), and Spleen 6 (Sp6) (Figure 2). Each of these points has well-documented analgesic action.[2,30] After the acupuncturist located each acupoint and disinfected it with isopropyl alcohol, a small plastic ring was placed over the acupoint and then covered with a thin sterile plastic tape. This served to blind the subjects to

Table 1A. Mean sensory ratings before acupuncture treatment ± SE for all subjects by session and temperature level

Session	Low (7-10)	Medium (11-14)	High (16-18)
3	9.2 ± 0.6	12.8 ± 0.5	16.5 ± 0.2
4	8.5 ± 0.6	12.1 ± 0.4	16.0 ± 0.3
5	8.3 ± 0.5	11.6 ± 0.4	15.6 ± 0.4

Intended range indicated in parentheses (n = 11 in each cell).

Table 1B. Mean affective ratings before acupuncture treatment ± SE for all subjects by session and temperature level (n = 11 in each cell)

Session	Low	Medium	High
3	6.0 ± 0.9	9.3 ± 1.1	13.8 ± 1.3
4	5.4 ± 0.8	8.3 ± 1.0	12.8 ± 1.3
5	5.2 ± 0.7	8.1 ± 1.0	12.2 ± 1.4

whether verum or placebo needles were used. Next, a 38-gauge sterile disposable stainless steel acupuncture needle was inserted into LI4, followed by St36, and finally Sp6 and manually manipulated by the acupuncturist to achieve the subjective *deqi* sensation.

Manual Acupuncture Procedure. Manual acupuncture needle manipulation was performed by use of a balanced tonifying and reducing technique at the 3 acupoints on the right side of the body in three 7-minute blocks, each separated by a 2-minute rest period (see Figure 2). During the 7-minute stimulation period, the acupuncturist manually stimulated one point for 30 seconds, followed by a 15-second break before moving to the next acupoint. Rotation frequency was approximately 180 rotations per minute at an angle of 45 degrees from the perpendicular to the skin surface.

Electro Acupuncture Procedure. After the 3 acupuncture needles were inserted and the *deqi* sensation was evoked, a surface ground electrode was placed 2 inches from each acupoint (for LI4, the electrode was placed on the palm facing the acupoint of LI4; for St36 and Sp6, the electrode was placed on the meridian below and above the acupoint, respectively). Wire leads connected each needle and ground electrode to an electro acupuncture device (OMS Medical Supplies IC-1107). The electrical intensity was determined individually for each subject by manual adjustment of the device by the acupuncturist. At the beginning of each block, intensity was increased gradually until the subjects felt the intensity was around a moderate level. During each 7-minute stimulation block, the current was continuously passed through the electrodes, with the frequency alternating between 2 Hz and 15 Hz every 30 seconds. Electro acupuncture was performed simultaneously at the 3 points on the right side of the body in three 7-minute blocks each separated by a 2-minute rest period (see Figure 2).

Placebo Acupuncture Procedure. Specially designed sham acupuncture needles,[20,29] visually indistinguishable from verum needles, but with a blunt tip and retractable shaft, were used. The needle tip stood on the surface but did not penetrate into the skin. The procedure for the placebo mode was identical to that for the electro acupuncture except that no current was passed through the electrodes. The acupuncturist went through the same motions of eliciting *deqi*, turning equipment knobs, etc, to maintain subject blinding.

Subjective Acupuncture Sensation Scale

Immediately after each acupuncture treatment, subjects were asked to quantify their sensations at each acupoint by rating the intensity with which they experienced each of 9 descriptive sensations. The sensations were stabbing, throbbing, tingling, burning, heaviness, fullness, numbness, soreness, and aching. These verbal descriptors were selected on the basis of traditional Chinese medicine descriptions of the *deqi* sensation in previous literature[1,31,37,39] and our experience. Because the deqi sensation is a very complicated subjective feeling, we expected that each individual would give different description and endorse a unique set of descriptors. As an important supplement, one blank row at the end of the 9 descriptors was provided and subjects were specifically told that if the descriptors did not accurately or completely describe the sensation they experienced, they should add their own words. Finally, subjects were asked to rate their degrees of anxiety during the acupuncture treatment. Each of the 11 elements on the Subjective Acupuncture Symptom Scale (SASS) (9 descriptors, 1 blank row, and the anxiety measure) was presented with a 10-cm bar with the anchor words "none," "mild," "moderate," and "severe" spaced evenly on the continuum. Subjects were asked to indicate their sensations for each element for each of the 3 acupoints with a hash mark anywhere on the continuum.

Data Analysis

Sensory and Affective Ratings. The analgesic effect of each of the 3 modes of acupuncture was determined by comparing the subjective ratings (sensory and affective) with identical noxious stimuli applied before and after acupuncture administration. We determined the difference between ratings for each preacupuncture and postacupuncture stimulus pair (matched for temperature, stimulus order, and limb). Analyses of variance (ANOVA) were conducted on this difference measure for the cohort. We fit full, fixed-effects ANOVA models separately for the sensory and affective ratings, including main effects and all interactions for the following factors: subject, acupuncture (verum vs sham), mode (manual vs electro), temperature level (low, medium, high), order of mode, limb (arm vs leg), laterality (treated/right vs untreated/left). We used fixed-effects models to understand the effects on this specific cohort. The significance level for the ANOVA models was $P < .0013$, Bonferroni corrected (.05/390).

Table 2A. Mean sensory ratings before and after acupuncture treatment ± SE for all subjects by mode across temperature levels (n = 11 in each cell)

	Low (7-10)		Medium (11-14)		High (15-18)	
	Before	After	Before	After	Before	After
Electro	8.5 ± 0.5	7.9 ± 0.6	11.8 ± 0.5	11.3 ± 0.6	15.6 ± 0.4	15.1 ± 0.6
Manual	8.9 ± 0.6	7.8 ± 0.7	12.5 ± 0.4	11.9 ± 0.4	16.3 ± 0.3	15.7 ± 0.4
Placebo	8.6 ± 0.7	8.6 ± 0.7	12.3 ± 0.5	12.4 ± 0.6	16.2 ± 0.3	15.9 ± 0.5

Table 2B. Mean affective ratings before and after acupuncture treatment ± SE for all subjects by mode across temperature levels (n = 11 in each cell)

	Low		Medium		High	
	Before	After	Before	After	Before	After
Electro	5.5 ± 0.8	4.9 ± 0.7	8.3 ± 1.1	7.7 ± 0.9	12.4 ± 1.3	11.7 ± 1.3
Manual	5.7 ± 0.8	4.7 ± 0.9	8.8 ± 1.1	8.3 ± 1.0	13.3 ± 1.3	12.5 ± 1.3
Placebo	5.4 ± 0.8	5.5 ± 0.9	8.6 ± 1.0	8.8 ± 1.2	13.1 ± 1.4	12.6 ± 1.4

To investigate the specific individual subject contributions to the overall analgesic effect, two separate ANOVA analyses were performed, each using a model with temperature level and treatment mode as factors, on the sensory rating data from each of the subjects. The first analysis modeled the effect of verum acupuncture (manual and electro) compared with placebo; the second tested for the difference between the two modes of verum acupuncture (significant effects for both analyses reported at $P < .05$).

Deqi Ratings. The subjective experience of each of the nine elements of the *deqi* sensation was quantified by measuring the distance in millimeters from the left end of the scale to the hatch mark indicated by each subject for each term. Quantified ratings (0.0-10.0) based on the 100-point scale were used to analyze the differences between acupuncture mode and acupoint. Ratings were averaged across subjects for each acupoint and for each treatment mode. In addition, an exploratory correlation analysis was performed between each of the SASS elements of the *deqi* sensation and the analgesic effect as determined by pain rating changes before and after treatment. The significance level for the corelation analysis was $P < .006$, Bonferroni corrected (.05/9).

Results

Subjects

Of the 31 volunteers who consented to the study, 11 (6 female) completed all five sessions. Subjects who did not demonstrate the psychophysical ability to reliably distinguish pain intensity were dropped from the study. Thirteen subjects did not meet criteria to proceed to Session 2; 5 did not meet criteria to proceed to Sessions 3 through 5 because of the unstable rating of calibrated pain stimuli, which was usually due to variability in the ratings of stimuli applied to the legs. Two subjects were dropped from the study because they had mild adverse responses to acupuncture (dizziness during acupuncture manipulation) in Session 2.

During the debriefing after Session 5, subjects were asked if they had noticed that any of the acupuncture treatments had been a placebo. None of the 11 subjects thought that they had received a placebo treatment, nor did any realize that the needles did not penetrate the skin in all treatments.

Subjective Ratings of Pain and Acupuncture

Stability of Subjective Ratings of Pain. Subjects who completed the study consistently reported stable sensory and affective ratings that correlated with the intensity of the stimuli before treatment (Tables 1A and 1B). Although there was a small but significant decrease in the sensory ratings across Sessions 3, 4, and 5, the ratings remained within the intended ranges throughout the three sessions.

Changes in Sensory and Affective Ratings Before and After Treatment. The group-averaged sensory and affective rating for three modes of treatment are shown in Tables 2A and 2B. The changes in sensory and affective ratings of pain stimuli (POST-PRE) after acupuncture treatment, averaged across the three temperature levels and four limbs, are shown in Figure 3.

The ANOVA of sensory pain ratings indicated that there were main effects of subject ($P < 1 \times 10^{-6}$), verum (manual or electro) acupuncture ($P < 6.0 \times 10^{-4}$), and limb ($P < 5.00 \times 10^{-4}$) (arms had greater analgesia than legs). Within the group, there was no difference between manual and electro acupuncture ($P < .1$). There were significant interaction effects between subject and

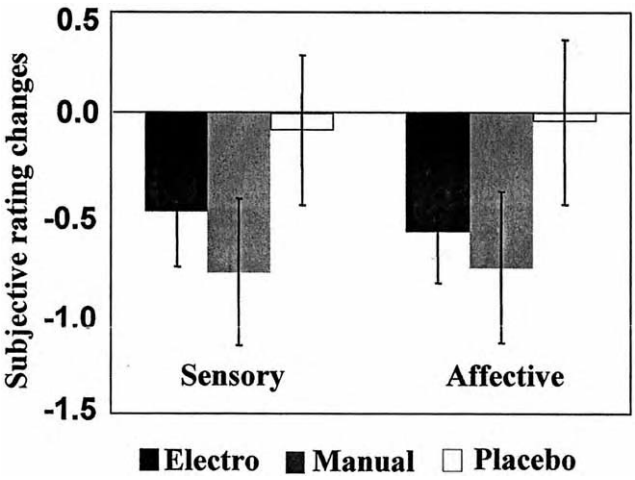

Figure 3. Sensory and affective rating changes after treatment. Differences between sensory and affective pain ratings before and after acupuncture treatment averaged across the three temperature levels and four limbs (n = 11, values are mean ± SE).

four other factors analyzed (acupuncture, mode, limb, and laterality) ($P < 2.8 \times 10^{-4}$).

An identical ANOVA on the affective ratings showed that there were main effects of subject ($P < 1 \times 10^{-6}$), verum (manual or electro) acupuncture ($P = 6.2 \times 10^{-5}$), and limb ($P < 3.2 \times 10^{-4}$) (arms had greater analgesia than legs). Within the group, there was no difference between manual and electro acupuncture ($P < .3$). The affective ratings exhibited greater variability and, in addition to the four subject interaction effects found in the sensory ratings, also showed a significant three-way interaction among mode of acupuncture, side of pain application, and temperature level ($P < 4.30 \times 10^{-4}$).

No effects were found for order of treatment mode, stimulus temperature level, or laterality (whether the pain was applied to the treated or untreated side) for either sensory or affective ratings.

Analysis of data from each individual showed that, of the 11 subjects who completed the study, 5 showed significant analgesic effects of verum acupuncture, with 3 subjects significantly responding to manual acupuncture and 2 subjects to electro acupuncture. Each of these 5 subjects had a small but highly significant analgesic effect (*P* values for the 5 subjects: .028, .022, .013, .002, 3×10^{-7}) to only one verum mode of treatment. The mean changes in sensory rating for these 5 responders averaged across temperature levels and limbs was 1.6 ± 0.5 and did not differ between the two verum modes. The magnitude of this suppression in ratings did not differ between arm and legs but showed a trend toward stronger analgesia on the right side than on the left side ($P <$ .09). There was also a trend for the subjects to be the most sensitive to the analgesia effect in response to the lowest of the three temperature levels; however, because of individual variability, this was not significant ($P <$ .08). Further, no subject had a statistically significant increase in pain ratings after any acupuncture treatment. There were no significant interactions between treatment mode and temperature level in any of the individual analyses.

SASS. Figure 4 presents the summary of the ratings for each of the nine descriptors on the SASS by mode and acupoint. Average ratings of each of the nine elements of the *deqi* sensation for each acupoint fell between 0.0 and 6.0 on the 10.0-point scale for all three modes of treatment. Individual ratings for the sensations spanned the 10.0-point scale (with highest score reported 9.1), but most ratings fell in the mild to moderate range (<5.0). We found relatively consistent ratings across the three acupuncture points within each mode, with highest ratings for tingling, numbness, soreness, and aching. Across all modes and acupoints, subjects reported a constellation of sensations, selecting an average of 5.17 ± 0.43 (mean ± SD) sensations out of the nine possible descriptors. The two verum modes of acupuncture produced appoximately equivalent ratings for all three acupoints. The average ratings for the placebo mode (1.3) were less than those for either the electro (2.4) or manual (2.2) verum modes. All subjects reported their experience of the *deqi* sensation using the nine terms presented in the SASS; no subject opted to add a term in the blank row provided.

Exploratory correlation analysis between the analgesic effect (difference in sensory pain ratings between posttreatment and pretreatment pain epochs) and each of the nine sensations quantified on the SASS revealed significant correlations with two scales: the numbness sensation ratings ($P < 9.0 \times 10^{-4}$) and the soreness sensation ratings ($P <$ .002) (Figure 5). The same results were noted when the analysis was performed for each mode separately.

Anxiety Ratings. The average subjective ratings of anxiety during treatment for each of the three acupoints across the three modes ranged from 0.4 to 1.5 on the 10.0 scale. Six of the 11 subjects reported anxiety ratings of 0 over all acupuncture points and modes. The ratings were consistent across points for each mode with average anxiety ratings of 1.3 for electro, 0.7 for manual, and 0.5 for placebo. There were no significant differences between the acupuncture modes.

Discussion

Our randomized pilot study in 11 healthy subjects showed that verum acupuncture (both manual and electro), but not placebo, lowered pain ratings to calibrated noxious thermal stimuli. There were significant interaction effects between subject and four other factors analyzed (acupuncture, mode, limb, and laterality), consistent with the interpretation that there was individual variability in response to acupuncture-induced analgesia. For example, some subjects showed a greater analgesic laterality effect ipsilaterally and others contralaterally, but averaging over the cohort, there was no significant laterality effect. Although we did not find a significant difference between the two verum modes in the group, individual ANOVA revealed that manual acu-

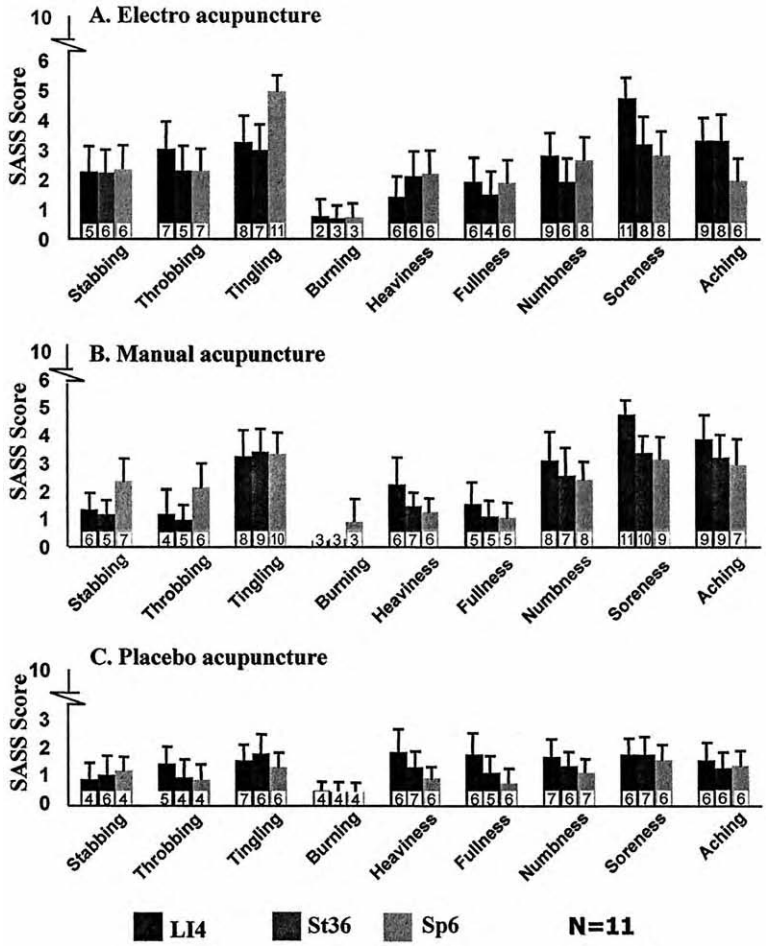

Figure 4. Acupuncture treatment is associated with a complex sensory experience. Group average results of the SASS show mild to moderate ratings (mean ± SD) for each acupoint and mode (electro **[A],** manual **[B],** placebo **[C]**). The numeral on each bar indicates the number of subjects out of 11 who rated that term above 0.

puncture resulted in significant analgesia in 3 subjects, whereas electro acupuncture resulted in significant analgesia in 2 others compared with placebo acupuncture treatment. These results are consistent with previous studies showing that verum acupuncture can produce detectable analgesia to experimental pain in healthy subjects as measured by sensory and affective ratings.[13,25]

Subjects reported equivalent average ratings of the *deqi* sensations evoked by the two verum modes of acupuncture. Although most subjects reported sensations during placebo treatment, the average ratings were lower than for the two verum modes. Importantly, subjects reported that they had either no or very low anxiety during any of the treatments, suggesting that stress is not likely to have contributed to the analgesia. Significant correlations between analgesia (difference in sensory pain ratings between posttreatment and pretreatment pain) and the SASS ratings of (1) numbness and (2) soreness, but not with the ratings of stabbing, throbbing, tingling, burning, heaviness, fullness, or aching, were found. This suggests that some attributes of the *deqi* sensation may be useful clinical indicators of effective treatment.

The question of whether certain individuals are "good" responders to acupuncture is important when clinical outcomes of acupuncture treatment are investigated. An equally important question is whether an individual's response to one modality of acupuncture will predict the response to another modality. In a previous study comparing treatment efficacy of different acupuncture modes (manual acupuncture and electro acupuncture at 2 Hz and 80 Hz) for chronic low back pain, Thomas and Lundberg[33] found that only electro acupuncture at 2 Hz produced significant improvement. However, their experimental design precludes within-subject comparisons of treatment mode efficacy. Although ours was not a clinical study, individual ANOVA results show that 5 of the 11 subjects had significant analgesia compared with placebo treatment after verum acupuncture, whereas the remaining 6 showed no measurable effect, suggesting that there were five "good" responders in our cohort. There were no systematic differences in the temperatures used during heat pain administration between these "good" responders and the rest of the cohort. Of the 5 responders in our study, 3 only showed significant analgesia after manual acupuncture, whereas 2 others only showed the effect after elec-

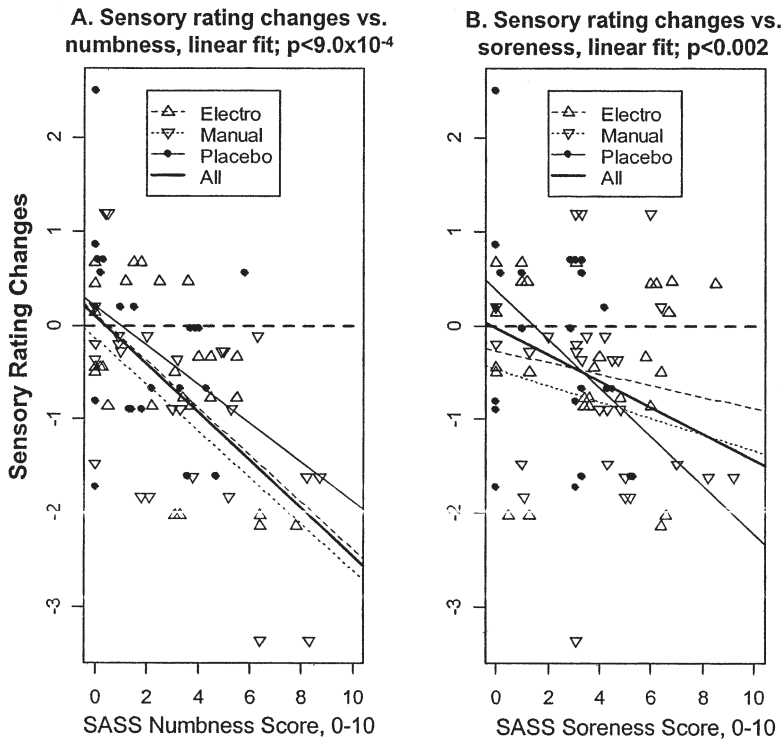

Figure 5. Treatment efficacy is correlated with ratings of numbness and soreness. Each graph shows the results of the correlation analysis of one element of the SASS (numbness **[A],** soreness **[B]**) with the difference in sensory pain ratings before and after treatment.

tro acupuncture. It is important to note that there is no evidence that responses to different modalities are mutually exclusive. The interpretation of these results is limited by our small sample size; however, the results demonstrate for the first time the existence of both individual and acupuncture mode variability, suggesting that acupuncture's analgesic effect on experimental pain may be dependent on both subject and mode.

This finding supports evidence that different mechanisms may underlie these two treatment modalities. For instance, recent functional brain mapping studies conducted during administration of manual and electro acupuncture in healthy subjects demonstrate distinct patterns of brain activation.[21,41,42] This was observed even when the same acupoint, LI4, was used in the same cohort of subjects.[21] As another example, manual and electro acupuncture treatment at a series of acupoints, including LI4, St36, and Sp6, had different effects on rates of resting and stimulated salivary flow in healthy subjects.[6] This differential effect on salivary flow rates has been associated with differential release of neuropepties.[5] These results, together with the observations in this study, suggest that manual and electro acupuncture may work through different mechanisms and, thus, may affect the same individual differentially.

Design of an adequate control condition is a major challenge in acupuncture research.[23,28,35,36,40] An appropriate control condition should be physiologically inert in that it must not activate any of the proposed mechanisms of acupuncture. The sham needle with the retractable shaft does not puncture the skin but provides a sensation on placement that is reported to be indistinguishable from the matched verum acupuncture needles.[20,29,40] This is a crucial development in acupuncture research because it fully controls for subject expectancy without puncturing the skin and potentially activating any of the hypothesized neural, endocrine, immune, or metabolic signaling pathways.[10,13,14,39] Previous studies of placebo acupuncture using a sham needle included manual manipulation of the sham needle to maintain subject blinding. Our novel method of administration addresses the argument that even manual manipulation without insertion at an acupoint can produce some treatment effect. Further, we had no need to manually manipulate the sham needle to protect subject blinding because our placebo mode was designed to mimic electro acupuncture in which minimal manual manipulation only occurs at the time of insertion.

Our simple assessment tool, the SASS, was useful in investigating the *deqi* sensation evoked by acupuncture needle manipulation. The SASS results confirm that the *deqi* sensation is complex, with all subjects using multiple descriptors for each acupoint during each mode. This fits with results reported by Vincent et al[37] in a large cohort of patients, further supporting the clinical observation that *deqi* is a complex sensory experience. In our study, because of the individual variability, no clear gender differences were noted in the SASS ratings. Further, there were no clear patterns in rating for "good" responders. The three acupuncture points tested, LI4, St36,

and Sp6, are all located deep (approximately 1 cm) in comparable tissue planes.[44] These three acupuncture points had comparable SASS profiles within and across subjects. Further investigation could verify what sensations would be reported on the SASS for acupoints with different tissue characteristics. Of note, no subject wrote in an additional sensation descriptor, suggesting that the SASS is effective in evaluating the *deqi* sensation in healthy, acupuncture-naive subjects. Since we completed our data collection, reports of another assessment tool that quantifies four aspects of the *deqi* sensation (dull/heavy, radiating, stinging, and electric) have been published.[27,40] It is notable that this assessment tool aggregates the term "numbness" with "heaviness" and, hence, might not have shown the correlation with analgesia.

We found a significant correlation between the analgesic effect and the ratings on numbness and soreness evoked by acupuncture treatment. With use of action potential recordings to categorize the nerve fibers involved in aspects of the *deqi* sensation, Wang et al[38] showed that numbness was conveyed mainly by $A\beta/\gamma$ fibers, distention and heaviness by $A\sigma$ fibers, and soreness by C fibers. Our findings suggest that multiple fiber types may participate in the analgesic effects of acupuncture, and further, that the experience of numbness or soreness during acupuncture treatment may be an important clinical correlate of analgesia irrespective of treatment modality. These observations must be interpreted with appropriate caution because they were made in a relatively small cohort of healthy subjects. Further testing in clinical populations is warranted.

Despite the small cohort, our study design afforded us sufficient statistical power to test our hypothesis, and this result is in line with previous reports and expectations, given the cohort and the nature of the experimental pain stimuli. First, we conducted a within-subjects comparison, allowing us to compare analgesic responses directly with the three modes of treatment within each individual. Second, we used experimental pain, which has been used in previous acupuncture analgesia studies and is more reliably comparable and controllable across subjects and sessions compared with chronic pain. Finally, we included pretreatment training sessions and established strict criteria to exclude subjects who were not able to rate the experimental pain stimuli reliably. This last element significantly reduced noise in the data that would have resulted from unstable pain ratings had we not included such rigorous training and screening in our study. These three aspects of our study design allowed us to detect significant analgesic effects of acupuncture in response to calibrated noxious stimuli.

This pilot study is limited by the small cohort size, which consisted only of healthy subjects able to reliably sense and report nonclinical pain. We want to emphasize here that the positive finding was clearly exploratory and that additional studies to examine the effect of acupuncture treatment on pain in clinical populations in larger sample sizes are necessary. This preliminary result may be of importance for the design of further confirmative studies. Improvements in study design for future clinical trials of acupuncture, such as validated tools for the subjective assessment of the *deqi* sensation and better sham control conditions, may confer greater sensitivity to detect true therapeutic effects of acupuncture.[43]

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Ambulatory Monitoring of Physical Activity and Symptoms in Fibromyalgia and Chronic Fatigue Syndrome

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Objective. **Fibromyalgia (FM) and chronic fatigue syndrome (CFS) are associated with substantial physical disability. Determinants of self-reported physical disability are poorly understood. This investigation uses objective ambulatory activity monitoring to compare patients with FM and/or CFS with controls, and examines associations of ambulatory activity levels with both physical function and symptoms during activities of daily life.**

Methods. **Patients with FM and/or CFS (n = 38, mean ± SD age 41.5 ± 8.2 years, 74% women) completed a 5-day program of ambulatory monitoring of physical activity and symptoms (pain, fatigue, and distress) and results were compared with those in age-matched controls (n = 27, mean ± SD age 38.0 ± 8.6 years, 44% women). Activity levels were assessed continuously, ambulatory symptoms were determined using electronically time-stamped recordings at 5 time points during each day, and physical function was measured with the 36-item Short Form health survey at the end of the 5-day monitoring period.**

Results. **Patients had significantly lower peak activity levels than controls (mean ± SEM 8,654 ± 527 versus 12,913 ± 1,462 units; $P = 0.003$) and spent less time in high-level activities when compared with controls ($P = 0.001$). In contrast, patients had similar average activity levels as those of controls (mean ± SEM 1,525 ± 63 versus 1,602 ± 89; $P = 0.47$). Among patients, low activity levels were associated with worse self-reported physical function over the preceding month. Activity levels were inversely related to concurrent ambulatory pain ($P = 0.031$) and fatigue ($P < 0.001$). Pain and fatigue were associated with reduced subsequent ambulatory activity levels, whereas activity levels were not predictive of subsequent symptoms.**

Conclusion. **Patients with FM and/or CFS engaged in less high-intensity physical activities than that recorded for sedentary control subjects. This reduced peak activity was correlated with measures of poor physical function. The observed associations may be relevant to the design of behavioral activation programs, because activity levels appear to be contingent on, rather than predictive of, symptoms.**

Fibromyalgia (FM) is characterized by diffuse pain and tenderness (1,2). Individuals who meet the criteria for FM (2) typically experience secondary symptoms including fatigue, sleep disturbances, and cognitive dysfunction (1–5). Because of the substantial overlap in clinical presentation and biologic correlates of the primary and secondary FM symptoms (6), many individuals with FM will also fulfill the criteria for chronic fatigue syndrome (CFS) (7,8), particularly in tertiary care centers (1).

Physical disabilities are common in individuals with FM and CFS, with self-reported functional limitations that are ~2 SD below the mean value for physical function in the general population (9,10). Lower physical activity levels may contribute to the onset and severity of symptoms (11–14), and exercise interventions result in symptom improvement in both FM and CFS (13,15–18). Causes of poor self-reported functional sta-

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tus are not well understood. Symptom status and psychosocial factors are partially predictive of self-reported physical function (10,19,20).

Most research examining determinants of physical function in FM/CFS is based on methods that may have inherent biases, because both symptoms and physical function have been recorded using retrospective, self-reported data. When asked to retrospectively report symptoms, individuals do not accurately integrate all their experiences over a given period of time; instead, there is a tendency to report peak symptoms and most recent symptoms (21). Moreover, individuals modify retrospective symptom reports on the basis of their symptoms and moods at the time of survey completion (22). To minimize this retrospective bias, the present study uses continuous, automated activity monitoring and repeated symptom assessments throughout the day.

Compliance and accuracy of the timing of symptom reports can be validated using an electronic storage device (21,22–26). These "real-time" symptoms can be crosstabulated with objective measures of physical activity obtained during the same periods of time. This method enables improved investigation of cause–effect relationships between activity levels and symptoms during activities of daily life. Little is known about these causal pathways in FM/CFS. For example, patients with FM frequently report that their symptoms worsen after high levels of activity, and that they are unable to perform activities because of symptoms. The longitudinal design of the electronic method permits evaluation of the short-term (within 30 minutes) relationship between activity and symptoms as well as the long-term association of aggregated daily activity levels and nocturnal restlessness with composite symptom measures (4,23,27). In the present study, we tested the hypotheses that FM/CFS is associated with reduced levels of daily activity and increased indices of disturbed sleep, and that high levels of activity are followed by increased symptoms.

PATIENTS AND METHODS

Patient selection. Patients (n = 38, mean ± SD age 41.5 ± 8.2 years, 74% women) were recruited through local newspaper and clinic advertisements. Inclusion criteria were the presence of the American College of Rheumatology diagnostic criteria for FM (n = 29) (2) and/or the criteria for CFS (n = 9) as defined by Fukuda et al (6). Consistent with prior observations (1), CFS often coincided with FM (21 [72%] of the 29 patients with FM, group concordance 55%) (Table 1).

Table 1. Characteristics of the study populations*

	Controls (n = 27)	Patients (n = 38)	*P*
Age, mean ± SD years	38.0 ± 8.6	41.5 ± 8.2	0.11
Sex, no. (%)			
Male	15 (56)	10 (26)	0.017
Female	12 (44)	28 (74)	
Race, no. (%)			
African American	8 (30)	8 (21)	0.19
Caucasian	11 (41)	24 (63)	
Other	8 (30)	6 (16)	
Height, mean ± SD meters	1.79 ± 0.11	1.66 ± 0.13	0.009
Weight, mean ± SD kg	77.2 ± 15.8	72.7 ± 12.8	0.33
Diagnosis, no. (%)			
Fibromyalgia + CFS	–	21 (55)	–
Fibromyalgia only	–	8 (27)	–
CFS only	–	9 (24)	–

* CFS = chronic fatigue syndrome.

Exclusion criteria were 1) severe physical impairment precluding ambulatory physical exercise (e.g., bilateral amputation, complete blindness); 2) medical conditions known to cause FM or CFS symptoms, including obesity (body mass index >30 kg/m^2), autoimmune/inflammatory diseases, cardiopulmonary disorders, chronic asthma, uncontrolled endocrine or allergic disorders (e.g., hypothyroidism, diabetes, allergic rhinitis), or malignancy; 3) current psychiatric disorders of schizophrenia, major depression with suicidal ideation, or substance abuse within 2 years; and 4) medication usage other than as-needed analgesics. Age-matched healthy, sedentary control volunteers (n = 27, mean ± SD age 38.0 ± 8.6 years, 44% women) were enrolled using the same exclusion criteria. To avoid confounding by high levels of routine exercise, controls were enrolled by excluding individuals who were participating in regular exercise programs.

Ambulatory activity assessments. Ambulatory physical activity levels were assessed using an actigraph accelerometer (Actiscore; Mini-Mitter, Bend, OR). The actigraph is a wristwatch-sized (37 × 29 × 9 mm), light-weight (17 gm) device that has been validated previously (28,29). Actigraphs contain a piezo-electric sensor that generates a voltage when the device undergoes a change in acceleration. The actigraph is most sensitive to movement perpendicular to the device. Actigraphs were placed on the wrist and, consequently, are most sensitive to the natural movements of the arm but adequately assess whole-body movements (28,30). The signal is amplified and digitized by the on-board circuit at 31.25-msec intervals, and stored in memory as activity counts. The device has a sensitivity of <0.01 G-force, and there is a linear relationship between activity counts and G-force (1 G-force = 251 counts; 100 G-force = 3,133 counts). Care was taken for proper placement of the actigraph by using a standardized mounting and positioning protocol (28).

Activity counts were recorded continuously and summed over 5-minute epochs. Peak and average activity levels were assessed across the 5-day observation period, with exclusion of missing data resulting from temporary removal of the actigraph.

Peak activity levels were defined as the highest level of activity in a 5-minute period during 1) the entire 5-day

Table 2. Comparison of physical activity levels in patients with fibromyalgia/chronic fatigue syndrome versus controls*

	Controls	Patients	*P*
Peak activity level, units	12,913 ± 1,462	8,654 ± 527	0.003
Average daily activity level, units	1,602 ± 89	1,525 ± 63	0.47
Time spent in specific activity levels, %			
High	1.3 ± 0.3	0.2 ± 0.1	0.011†
Moderate	14.8 ± 1.5	13.6 ± 1.4	
Low	38.7 ± 1.6	42.8 ± 1.2	
Very low	45.8 ± 2.8	43.9 ± 2.0	

* Except where indicated otherwise, values are the mean ± SEM (not adjusted for sex and age).
† Main effect for group differences on log-transformed ratios (Wilks' lambda = 0.834, F[3,61] = 4.057). Component analysis of log-transformed ratios yielded significant differences ($P < 0.01$) for % time spent in high-level activity only (see text for details).

observation period (Table 2), and 2) within each of the specific episodes throughout the day. Specific episodes were defined as morning (first hour after waking up), mid-morning (1 hour postawakening until lunch), afternoon (between lunch and 3:00–4:00 PM), and evening (between 3:00–4:00 PM until 30 minutes before going to bed) (Figure 1). Each episode (e.g., morning) was composed of multiple 5-minute segments, in which each of these segments consisted of a cumulative count of activity units. For each patient, we examined the epoch with the highest value to determine peak activity level. Peak activity levels were not averaged across days, but absolute peak values irrespective of the day of observation are reported in Table 2 and Figure 1.

Average activity levels were calculated using parallel procedures 1) over the entire 5-day observation period (Table 2), and 2) within each of the 4 specific episodes throughout the day (morning, mid-morning, afternoon, and evening). Average values across all 5-minute epochs within each episode (e.g., morning) were calculated, and those averages were subsequently averaged over the 5-day period. For example, for the 60-minute morning episode (from waking up until 1 hour postawakening), a total of twelve 5-minute epochs were examined; the peak activity level was the highest value among the twelve 5-minute epochs on 1 of the 5 observation days, and the average activity for that episode was calculated as the average over the 12 values, which was then averaged over the 5-day observation period.

In addition, registrations were made of the duration (as a percentage of time spent) in high-level activities (>8,000 units/5 minutes; e.g., running, gardening), moderate-level activities (>3,000–8,000 units/5 minutes; e.g., effortful walking), low-level activities (1,000–3,000 units/5 minutes; e.g., office work, minimal physical activity), and very-low activity levels (<1,000 units/5 minutes; e.g., sitting still, lying down). The percentage of time spent in high-level activities was used as an additional measure to avoid potential biases resulting from chance observations resulting from a (very high) single 5-minute period.

Assessment of ambulatory sleep parameters. To document differences between patients and controls in sleep parameters, we assessed the duration of sleep, restlessness during sleep, and sleep efficiency. Wake-up time and sleep time were based on patients' self reports and were validated using actigraphy data. Based on prior validation studies, patients were deemed awake when activity exceeded 50% of the average daytime activity level and asleep when activity levels reached 50% below patients' average nocturnal level. Average nocturnal activity levels were assessed for each night and averaged across the 4 nights of observation. The sleep fragmentation index was also used as a second, actigraph software–based indicator of restless sleep, calculated as follows: (% 1-minute intervals of movement during sleep + % 1-minute intervals of immobility) divided by total 1-minute immobility intervals (Mini-Mitter). Sleep latency was defined as the time between going to bed and actual sleep start, which was determined as the first 10-minute span of immobility (<40 counts per minute). Sleep efficiency, used as a measure of sleep quality, was defined as follows: (time in bed spent asleep divided by total time in bed) multiplied by 100 (Mini-Mitter).

Ambulatory symptom assessments. *Symptom ratings.* Patients and controls rated symptom severity at 5 time points during the day over a consecutive 5-day period. Self-reports of pain, fatigue, and stress levels were made on a 10-point scale, with higher scores indicating more symptoms. We have used similar strategies for ambulatory symptom assessments in patients with cardiac disease (31). Real-time assessments of symptoms are superior to retrospective symptom reports in many clinical settings because such evaluations are not influenced by recall biases (25). Symptom ratings were made using the actigraph keypad to improve compliance and allow for validation of accurate time of entry (22,26). Patients were instructed to complete symptom reports at 5 time points: 1) upon awakening prior to getting out of bed, 2) 1 hour after waking up, 3) before lunch, 4) late afternoon between 3:00 and 4:00 PM, and 5) 30 minutes before going to bed. To optimize compliance of symptom monitoring during daily activities, the actigraphs prompted patients with 3 alerts that were preset based on usual wake-up time (1 hour post-, 5 hours post-, and 9 hours postawakening). The first and last entries were not accompanied by an alert in order to minimize interference with patients' usual sleep–wake patterns.

Retrospective self-reports of pain and fatigue. To examine the validity of the ambulatory symptom assessments, each patient's average and peak symptom ratings over the 5-day period were correlated with standard self-reported measures of perceived physical function and quality of life as determined on the Short-Form 36 (SF-36) health survey (32). The SF-36 was administered after completion of the 5-day ambulatory observation period and refers to symptoms experienced during the past month. Subscales of the SF-36 include physical functioning, social functioning, physical role, emotional role, mental health, vitality, bodily pain, and general health. The SF-36 is routinely used to evaluate the impact of medical conditions on patients' quality of life, with higher scores indicating better quality of life (i.e., less dysfunction). The purpose of cross-tabulating the SF-36 with ambulatory measures was to examine the correspondence between prospective ambulatory assessments of pain and fatigue with retrospective symptom reports based on the SF-36, and to examine whether physical activity levels were differentially predictive of prospective versus retrospective symptom reports.

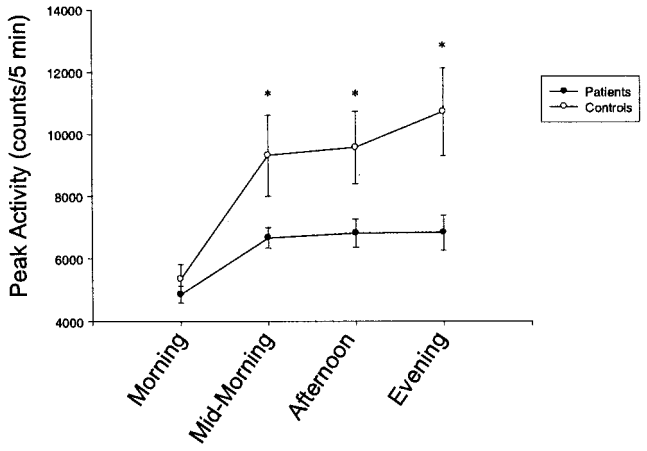

Figure 1. Diurnal variation in peak physical activity levels (counts per 5-minute [5 min] intervals), comparing patients with fibromyalgia/chronic fatigue syndrome (n = 38) with healthy sedentary controls (n = 27) during 4 phases of the day: 1) Morning (first hour after waking up), 2) Mid-Morning (1 hour postawakening until lunch), 3) Afternoon (between lunch and 3:00–4:00 PM), and 4) Evening (between 3:00–4:00 PM until 30 minutes before going to bed). All time segments were corrected for patients' individual wake-up times. Bars show the mean ± SEM. * = $P < 0.05$ versus patients.

Statistical analysis. Average and peak activity levels were calculated throughout daytime episodes, and results are presented as the mean ± SEM activity counts (in units per 5-minute epoch). Analysis of variance (ANOVA) was used to compare patients with controls. Because the groups were not matched for sex, analyses of covariance were conducted to adjust for potential effect modification related to sex. Differences in variability between groups were examined using Levene's test for equality of variance. Variances were not pooled across groups for *t*-test calculations if between-group variances were significantly different. To examine group differences in the percentage of time spent in various levels of activity, multivariate ANOVA was used to compare patients and controls on log-transformed ratios of percentages of time spent in each level of activity.

Symptom exacerbation and amelioration were evaluated by examining patients as their own controls. Mixed-effects modeling was used to examine relationships between activity levels and symptoms among patients, using day and time of observation as repeated measures and subject as the random factor. Lagged crosscorrelation coefficients were used to determine whether changes in activity levels preceded or followed changes in symptoms of pain and fatigue.

RESULTS

Patient characteristics. The characteristics of the patients and controls are presented in Table 1. Men displayed higher peak activity levels ($P = 0.014$) and higher nocturnal activity levels ($P = 0.05$) than did women. After statistical adjustments for sex, none of the other demographic control measures were related to activity levels.

Daily activity levels in FM/CFS patients versus controls. Table 2 shows that patients had significantly lower peak activity levels compared with controls (mean ± SEM 8,654 ± 527 units versus 12,913 ± 1,462 units; $P = 0.003$). Peak activity levels did not differ ($P = 0.78$) between patients with combined FM and CFS (n = 21; mean ± SEM 8,744 ± 712 units) and patients with either FM only (n = 8; 7,959 ± 974 units) or CFS only (n = 9; 9,064 ± 1,284 units). In contrast to the observed differences in peak activity, average physical activity levels did not differ between patients and controls (Table 2).

As shown in Figure 1, peak activity levels displayed diurnal fluctuations ($P < 0.001$), and patients had lower activity levels throughout the day compared with controls (P between groups = 0.005; P for interaction = 0.020), except during the first hour upon awakening. Diurnal activity fluctuation did not vary across the 5 days of observation. Individual differences in peak activity levels were larger among controls than among patients, as indicated by significantly larger variability of peak activity among controls compared with patients ($P < 0.05$) (Figure 1).

Patients spent significantly less time in high-level activities compared with controls (mean ± SEM 0.2 ± 0.1% versus 1.3 ± 0.3%; $P = 0.001$). Statistical log-transformed ratio analysis of the 4 levels of activity examined simultaneously confirmed that patients spent significantly less time in high-level activities (overall $P = 0.011$).

Statistical adjustment for sex and age did not alter these results. Patients still had lower peak activity levels (adjusted mean 8,989 ± 901 units in patients versus 12,443 ± 1,078 units in controls; $P = 0.020$) and spent less time in high-level activities (0.3 ± 0.2% versus 1.2 ± 0.2% in controls; $P = 0.007$).

Sleep efficiency. Patients had longer mean sleep latency time (an indicator of disturbed sleep) than did controls (mean ± SEM 20.0 ± 22.9 minutes versus 10.8 ± 13.6 minutes; $P = 0.051$). No differences were found in total duration of sleep. After statistical adjustment for sex and age, patients displayed more activity during sleep ($P = 0.050$), less sleep efficiency ($P = 0.076$), longer sleep latency ($P = 0.049$), and a nonsignificantly elevated sleep fragmentation index ($P = 0.17$) as compared with controls (Table 3).

Table 3. Nocturnal sleep characteristics in patients with fibromyalgia/chronic fatigue syndrome and controls*

	Controls	Patients	*P*
Sleep duration, minutes	438.1 ± 16.1	425.8 ± 12.6	0.560
Average nocturnal activity level	84.6 ± 17.6	130.1 ± 13.5	0.050
Sleep fragmentation index	12.0 ± 1.9	15.5 ± 1.5	0.170
Sleep latency, minutes	9.6 ± 4.3	20.7 ± 3.3	0.049
Sleep efficiency level	86.8 ± 1.8	82.6 ± 1.4	0.076

* Except where indicated otherwise, values are the mean ± SEM (sex- and age-adjusted). See Patients and Methods for details of sleep characteristics.

Ambulatory activities and symptoms of patients in relation to self-reported function. Ambulatory peak activity levels had a positive correlation with better self-reported physical function as determined by higher SF-36 scores (physical role r = 0.45, physical function r = 0.30; both $P < 0.05$), but there was no significant association between peak activity levels and self-reported pain (r = 0.21, $P = 0.22$) or general health (r = 0.22, $P = 0.35$). Associations between average activity levels and self-reported physical function were in the same direction, but were statistically nonsignificant ($P > 0.1$).

Ambulatory symptom reports were significantly correlated with retrospective self-reported SF-36 measures of physical function, and these displayed satisfactory divergent validity. Specifically, average pain reports during ambulatory monitoring were associated with SF-36–reported pain (r = −0.60, $P < 0.001$) and physical function (r = −0.47, $P = 0.004$), but not with physical role or general health. Negative correlation coefficients were in the expected direction, reflecting that higher SF-36 values, indicative of less dysfunction, are associated with fewer ambulatory symptoms. Ambulatory fatigue measures were not related to indices of health on self-report ($P > 0.10$). Ambulatory distress was associated with the SF-36 emotional role subscale scores (r = −0.31, $P = 0.04$) but not with other self-reported measures. Analyses of peak symptoms during ambulatory monitoring revealed similar results, with lower correlation coefficients for the associations.

Activity levels of patients in relation to ambulatory symptoms. Figure 2 shows that average and peak symptoms (pain, fatigue, and distress) were consistently elevated among patients versus controls throughout the day ($P < 0.01$). We examined whether short-term associations existed between activity levels and subsequent symptoms (in the range of 30–0 minutes prior to symptom assessment, using 5-minute segments). Averaged activity levels over the 30-minute period prior to symptom assessment were better predictors of symptom ratings than were assessments made over shorter, separate 5-minute segments. Proximal 5-minute segments (in the −15 minutes to 0 minutes range prior to symptom report) did not reveal stronger relationships with symptom ratings than more distal segments (range −30 minutes to −15 minutes) (data not shown).

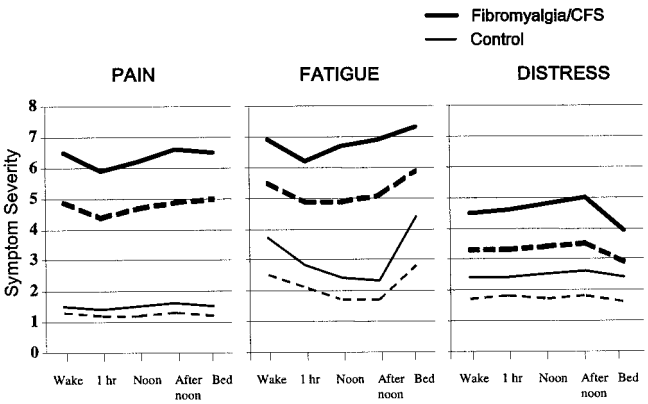

Figure 2. Diurnal variation in peak (**solid lines**) and average (**broken lines**) symptoms, comparing fibromyalgia/chronic fatigue syndrome (CFS) patients (n = 38) with healthy sedentary controls (n = 27) during 5 wake-time–adjusted time points throughout the day. Standard errors (not shown) varied from 0.07 to 0.44. Peak levels indicate the maximum symptom rating in that particular time point, as reported on 1 of the 5 observation days, and were higher in patients than in controls (all $P < 0.01$).

Mixed-effects modeling revealed that 30-minute activity levels were negatively correlated with pain ($P = 0.031$) and fatigue ($P < 0.001$), and positively correlated with distress ($P < 0.001$). Table 4 presents bivariate correlations between average 30-minute activity levels with subsequent symptom ratings at the 5 points of assessment throughout the day. Consistent with the

Table 4. Correlation between 30-minute activity levels and subsequent symptoms throughout the day*

	Ambulatory symptom report		
Activity level	Pain	Fatigue	Distress
Upon awakening	−0.09	−0.09	−0.05
One hour after waking up	−0.08	−0.16†	−0.03
Before lunch	−0.21‡	−0.22‡	0.07
Late afternoon	−0.16†	−0.09	0.22‡
30 minutes before going to bed	−0.11	−0.12	0.07

* Values are bivariate correlation coefficients. Negative correlations indicate that lower activity levels are related to higher levels of symptoms.
† $P < 0.05$.
‡ $P < 0.001$.

Table 5. Crosscorrelation analysis examining lagged associations between activity levels and symptom reports*

	Ambulatory activity level		
Symptom	Activity preceding symptom report	Activity concurrent with symptom report	Activity following symptom report
Pain	−0.04	−0.12†	−0.12†
Fatigue	0.01	−0.17†	−0.16†
Distress	−0.01	0.10†	−0.02

* Values are lagged crosscorrelation coefficients. Negative correlations indicate that lower activity levels are related to higher levels of symptoms.
† $P < 0.05$.

mixed-model analysis, pain and fatigue were negatively correlated with activity levels, indicating that the activity levels were lower among individuals with higher levels of these symptoms, whereas distress displayed positive associations with activity levels, particularly during midday observations.

Lagged crosscorrelational analyses were performed to examine whether activity was a predictor of subsequent pain and fatigue ratings, whether associations were primarily concurrent, or whether pain and fatigue preceded subsequent activity levels. As shown in Table 5, the results suggest that fatigue was associated with lower concurrent and subsequent activity levels ($P < 0.05$), whereas activity levels were not predictive of subsequent fatigue. A similar pattern of results was found for lagged crosscorrelations of ambulatory activity levels with pain.

DISCUSSION

Using objective assessments of physical activity, this study documents that patients with FM and CFS have markedly reduced levels of peak activity, whereas average activity levels are not different from those of sedentary control subjects. Peak activity, but not average activity, also has an association with self-reported measures of physical function, suggesting that patients are reporting their inability to engage in high-level activities when completing such questionnaires. Symptoms such as pain and fatigue are associated with lower concurrent and subsequent activity levels. In contrast, activity levels are not a predictor of subsequent symptoms. These results may be particularly relevant to the design of behavioral activation programs, because activity levels appear to be contingent on, rather than predictive of, symptoms of pain and fatigue during activities of daily life.

Ambulatory monitoring techniques can be useful in the assessment of patients with FM and CFS, because these assessments provide unique information about the interrelation between activities and symptoms as they occur in patients' actual circumstances of daily life. Physical activity levels are recorded more accurately using ambulatory activity monitoring as compared with retrospective self-report (23,24). The present observations indicate that peak, but not average, daytime activity levels are reduced in FM/CFS patients versus controls, which is consistent with the findings in previous literature (23,27). Korszun and colleagues used ambulatory actigraphy to show that FM patients have similar mean daytime activity levels as that of controls, and also noted evidence of sleep disturbances in those with FM (23). However, our study is the first to perform complex, repeated-measures analyses of the results of ambulatory actigraphy and symptom reports, and we document clear differences between FM/CFS patients and controls with respect to peak activity levels and symptoms. In addition, no differences were found in ambulatory activity levels between patients with a primary diagnosis of FM and patients with a primary diagnosis of CFS. This observation may reflect the common phenotypic presentation of FM, CFS, and other chronic multisymptom illnesses (1,7).

The finding that individuals with FM and CFS have lower peak activity levels may help explain why patients with FM and CFS rate their physical function as being poor. Studies examining self-reports of other symptoms, such as pain, have demonstrated that when individuals are asked to retrospectively report pain levels over a period of time, their recall is biased by the most severe pain experienced during that period, so that the self-reported pain does not reflect a true "average" pain experience (33,34). In contrast to these prior observations, the present study revealed that the *average* ambulatory symptom levels, when collected reliably using electronic time-stamps, were slightly better predictors of retrospective self-reported measures when compared with *peak* ambulatory symptom levels. Ambulatory peak *activity* levels were better predictors of retrospective self-reported physical function, but not with retrospective pain reports. Further studies with larger sample sizes are needed to evaluate whether ambulatory recording techniques can be used to further improve the reliability of symptom assessments in patients with chronic pain and fatigue.

Our findings regarding actigraphy assessment of sleep function corroborate other available data regarding sleep in FM/CFS (3,4,35,36). Some studies have

suggested that restful sleep in patients with FM is followed by reduced pain and fatigue upon awakening (3,35). The present study revealed higher levels of pain and fatigue upon awakening as compared with later hours in the morning. We also found evidence of longer sleep latency, reduced sleep efficiency, and more movement during sleep among patients versus controls. However, no significant associations were observed between sleep measures and subsequent reports of pain or fatigue (results not shown). A dissociation between self-reported sleep measures and objectively assessed sleep patterns as they relate to symptoms has been reported by other investigators as well (37). The lack of association between sleep and subsequent symptoms may reflect selection criteria (patients were not preselected to have sleep disorders) and restriction of range (pain and fatigue ratings were consistently high throughout the day).

Our third hypothesis postulated that bouts of exercise would be followed by increased pain and fatigue. No support was found for such an association. This study confirms a prior report by Sisto et al (14), in which ambulatory activity levels assessed 1 week following maximal exercise testing were not lower than activity levels assessed during the preceding week. We did find that symptoms of fatigue and pain were predictive of a subsequent reduction in activity levels. It is possible that patients avoided high-intensity activity levels during their usual activities of daily life, thereby precluding evaluation of the effects of high-intensity activity levels on subsequent symptoms. These results may therefore not be generalizable to patients engaging in intensive exercise or those participating in structured exercise programs. Nonetheless, high activity levels did occur and were not followed by substantial increases in pain or fatigue. Thus, the present findings suggest that high-level activities do not necessarily lead to an increase in symptoms, and support the notion that exercise or behavioral activation programs should address fear or avoidance of physical activity.

There are several potential limitations regarding the interpretation of the present findings. First, participants in this research study may not be representative of the larger populations of FM patients. Nonetheless, demographic and symptom severity data in the present study are comparable with those noted in other studies in this spectrum of disorders. Second, combining FM and CFS patients could be a potential limitation of this study. We elected to examine both groups because of the substantial overlap in clinical presentation (55% of the participants had both conditions even though they were selected on the basis of a single diagnosis), similar behavioral and neurobiologic correlates, and parallel responses to exercise interventions. Consistent with this perspective, no differences were found in activity levels when comparing FM with CFS. A third potential limitation of this study is the reliance on statistical techniques, instead of experimental manipulations of physical activity, to assess the relationship between activity levels and symptoms. This approach precludes control over the level of exercise, and is limited by the fact that both symptoms and activity levels are significantly autocorrelated. Finally, these results may not be directly transferable to clinical settings involving exercise interventions, because patients were assessed during usual activities, not in the setting of specific exercise instructions.

In summary, this study shows that when FM/CFS patients are compared with control subjects with similar overall activity levels, they have reduced peak levels of activity and no consistent exacerbation of symptoms after periods of increased activity. This suggests a vicious cycle whereby symptoms may lead to inactivity, and inactivity (via both neurobiologic and psychological mechanisms) leads to increased symptoms. Patients attribute exacerbations of symptoms to a wide range of factors, including exercise, and therefore, fear or avoidance of increased activity and exercise may occur and further reinforce this cycle (38). Future mechanistic and interventional studies will be necessary to confirm these findings, and to determine if more effective interventions can be designed to simultaneously target physical activity and symptom management.

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The Development of Persistent Pain and Psychological Morbidity After Motor Vehicle Collision: Integrating the Potential Role of Stress Response Systems Into a Biopsychosocial Model

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Objectives: Persistent pain and psychological sequelae are common after motor vehicle collision (MVC), but their etiology remains poorly understood. Such common sequelae include whiplash-associated disorders (WAD), fibromyalgia, and posttraumatic stress disorder (PTSD). Increasing evidence suggests that these disorders share overlapping epidemiologic and clinical features. A model is proposed in which central neurobiological systems, including physiologic systems and neuroanatomical structures involved in the stress response, are an important substrate for the development of all 3 disorders and interact with psychosocial and other factors to influence chronic symptom development. **Methods:** Epidemiologic and clinical characteristics regarding the development of these disorders after MVC are reviewed. Evidence suggesting a role for stress response systems in the development of these disorders is presented. **Results:** Contemporary evidence supports a model of chronic symptom development that incorporates the potential for interactions between past experience, acute stress responses to trauma, post-MVC behavior, and cognitive/psychosocial consequences to alter activity within brain regions which process pain and to result in persistent pain, as well as psychological sequelae, after MVC. Such a model incorporates factors identified in prior biopsychosocial theories and places them in the landscape of our rapidly developing understanding of stress systems and CNS pain-modulating pathways. **Conclusion:** New models are needed to stimulate deeper examination of the interacting influences of initial tissue damage, acute pain, psychosocial contingencies, and central stress pathways during chronic symptom development after MVC. Deeper understanding could contribute to improved treatment approaches to reduce the immense personal and societal burdens of common trauma-related disorders. **Key words:** whiplash-associated disorders, pain, trauma, stress, fibromyalgia, PTSD.

CRH = corticotrophin-releasing hormone; **MVC** = motor vehicle collision; **WAD** = whiplash-associated disorders; **PTSD** = posttraumatic stress disorder; **HPA** = hypothalamic-pituitary-adrenal; **LC/NE**=locus ceruleus/norepinephrine-sympathetic.

INTRODUCTION

Among survivors of motor vehicle collision (MVC), persistent symptoms are common even after "minor" collisions and result in tremendous patient suffering and societal costs (1–4). These symptoms often present as psychological disorders, such as posttraumatic stress disorder (PTSD) (2,3). However, a substantial portion of post-MVC morbidity also involves chronic pain syndromes. Whiplash-associated disorders (WAD) are the prototypical MVC-related pain disorders, but fibromyalgia, with its more widespread pain, can also be triggered by MVC (5). For each of these disorders, the transition from acute injury to chronic illness remains poorly understood.

During the past 2 decades, considerable advances have been made in developing biopsychosocial models to describe the transition from acute injury to chronic pain. These advances utilized novel conceptualizations of cognitive-behavioral factors, such as pain-related fear and avoidance (6), which appear to influence the development of chronic pain in many individuals. The cyclical process whereby pain produces fear, which leads to behavioral avoidance, inactivity, disability, and increased focus on pain avoidance, is well-described in the Vlaeyen's model of chronic pain pathogenesis (6) (Figure 1). In a recent amendment of this model, Norton and Asmundson (7) emphasized the importance of physiologic activities that increase pain (eg, via increased muscle tension) and augment normal physiologic processes (eg, cause increased heart rate), which are then interpreted catastrophically. This later concept is rooted in an extensive literature on a cognitive etiology for panic disorder (catastrophic misinterpretation of bodily sensations) (8).

The ability of psychological factors to influence the development of chronic pain by shaping behavior and amplifying peripheral sensations, as highlighted in these models, is well supported by considerable research (6,7). However, there is increasing evidence that specific neurobiological mechanisms within central stress systems may participate in this process, derailing recovery and mediating progression to chronicity. These mechanisms have been most thoroughly examined in studies of PTSD but may be equally relevant to the development of chronic pain syndromes. Indeed, evidence suggests that PTSD and chronic pain disorders after trauma have many common links. The objective of this review is to examine available evidence that centrally controlled stress response systems can influence the development of all three conditions—WAD, fibromyalgia, and PTSD—after MVC and to suggest that insights from the PTSD literature may enhance our understanding of the development of WAD and fibromyalgia after MVC. An expanded biopsychosocial model for the development of posttraumatic pain syndromes is proposed that emphasizes the importance of interactions between central neurobiological processes and identified cognitive-behavioral factors during their development.

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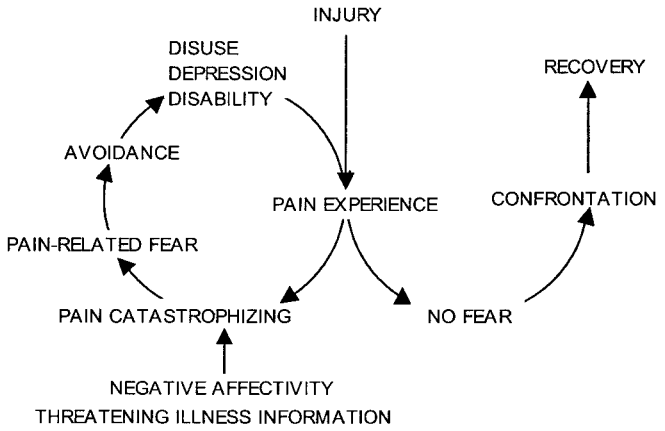

Figure 1. Vlaeyen's cognitive-behavioral model of chronic pain pathogenesis (Source: Vlaeyen JWS, Linton SJ. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. Pain 2000;85:317–332.)

WAD, FIBROMYALGIA, AND PTSD AFTER MVC

WAD are common after MVC, with symptoms that include pain in the neck, shoulder, or arm; headache; jaw pain; dizziness; tinnitus; and cognitive difficulties (9). Although some consider whiplash to be biomechanical in etiology (10), there is ample evidence that in many individuals WAD is not caused by biomechanical mechanisms alone. First, there is great variation in the prevalence of WAD among different populations (eg, high in North America (1) but very low in Greece (11)). Second, decreasing the financial benefit of developing whiplash syndrome improves WAD outcomes. The incidence of WAD decreased as much as 40% in Saskatchewan, Canada, when the providence changed from a tort-compensation system to a no-fault system (1). Third, collisions that occur in other settings (eg, in bumper cars) exert the same biomechanical stress as a low-speed MVC (12), yet prolonged WAD after bumper car collisions are rare (13). Fourth, there is no clear "dose effect" between trauma intensity and the likelihood of developing WAD (14,15). Although the severity of initial symptoms is an important predictor of chronic pain (15–17), the assumption that initial symptoms are proportional to initial tissue injury has not been validated. In an interesting experimental approach to this issue, Castro et al. (18) exposed patients to a "sham" rear-end collision. Twenty percent of subjects reported whiplash symptoms 3 days later, despite no actual collision.

Fibromyalgia is a common clinical syndrome defined by the presence of chronic widespread pain and tenderness (19) Fibromyalgia also occurs as a sequela of MVC, although its MVC-related incidence rate is less well defined. An anecdotal association between MVC and fibromyalgia symptom onset has long been reported: between 24% and 47% of fibromyalgia patients report that an MVC triggered the onset of their illness (20,21). A recent prospective, multisite study of fibromyalgia development after MVC found that among 224 subjects reporting neck pain after MVC, 3% developed fibromyalgia, as opposed to only 0.4% of 643 patients presenting to the emergency department for treatment of (non–MVC-related) minor laceration (5). The unadjusted relative risk of developing fibromyalgia among those initially presenting with neck pain after MVC versus those with laceration was 8.4. The cumulative direct and indirect evidence for a causal relationship between MVC and fibromyalgia exceeds that of other rheumatologic conditions for which an environmental trigger has been accepted (22).

PTSD, the prototypical stress-related disorder, is also common after MVC. To meet criteria for the diagnosis of PTSD, an individual must have 3 distinct types of symptoms related to the MVC event for at least 1 month: reexperiencing the event (eg, psychological distress on exposure to reminders), avoidance of reminders of the event, and hyperarousal (23). Multiple studies suggest that 10% to 16% of patients presenting to the emergency department after MVC will have PTSD 1 year later (2–4). As described below, there is increasing evidence that dysregulation within central stress response systems may play a critical role in the development of PTSD.

THE STRESS RESPONSE SYSTEM AND ITS PUTATIVE ROLE IN THE DEVELOPMENT OF PTSD AFTER MVC

Multiple mechanisms have been proposed by which abnormal stress system function during or after a stressor might increase the risk of PTSD development by disrupting the neurobiological processes which orchestrate an adaptive stress response. Acute stressors trigger the release of corticotrophin-releasing factor, which initiates the activation of the hypothalamic-pituitary-adrenocortical (HPA) axis and is a modulatory neurotransmitter within the locus ceruleus/norepinephrine-sympathetic (LC/NE) system, shaping the release of cortisol and epinephrine (24). These and other factors both help optimize one's ability to respond to the stressor and, importantly, modulate remembering of the event ("memory consolidation") (25). Pitman hypothesized that an exaggerated stress response (increased catecholamines and other neuropeptides) might lead to "overconsolidated memories" contributing to the development of PTSD (26). Consistent with this theory, increased heart rate after MVC (reflecting increased sympathomimetic response) has been found to predict the later development of PTSD (27–29). In addition, 2 recent preliminary studies have found that a pharmacologic intervention (propranolol) provided in the emergency department to attenuate the sympathomimetic response decreases the development of PTSD symptoms (30,31). Randomized controlled trials of this intervention are currently ongoing.

Cortisol enhances memory consolidation for emotionally adverse experiences (32), and thus increased cortisol levels after a stressor might be expected to increase the risk of PTSD development. Consistent with this, increased cortisol levels have been found to increase the risk of PTSD in children experiencing MVC (33). However, cortisol also inhibits memory retrieval (32,34), which may help prevent recurrent recollections of the traumatic event (memory reinforcement) during the postevent period, limiting memory formation and stress system activation (26). In addition, cortisol helps con-

tain the acute stress response by down-regulating adrenergic hormone release (35), which might also indirectly contribute to PTSD prevention (36). Three studies of cortisol response in adults after MVC have found that low cortisol levels increase PTSD risk (37–39). In addition, 2 randomized controlled trials have found that hydrocortisone administration in the intensive care unit during stressful events (cardiac surgery and sepsis) decreases subsequent PTSD development (40,41). In summary, although there are conflicting data and disagreements within the field about the precise role of cortisol as a risk factor for PTSD, it does seem clear that HPA axis function, like LC/NE system function, is an important factor in creating or identifying vulnerability and/or in shaping the progression of this stress disorder.

THE POSSIBLE ROLE OF STRESS RESPONSE SYSTEMS IN THE DEVELOPMENT OF PERSISTENT PAIN AFTER MVC

As described above, the possible role of stress response systems in the development of PTSD after stressful events continues to be extensively examined. However, the possible role of stress systems in the development of persistent pain after MVC has not been considered, and the possible mechanisms by which stress systems may interact with cognitive-behavioral factors and provide a common substrate for the production of both persistent pain and psychological sequelae have not been explored.

Multiple lines of evidence support the hypothesis that stress response systems are involved in the pathogenesis of chronic pain, as well as psychological sequelae after MVC: (1) WAD, PTSD, and fibromyalgia have overlapping epidemiologic and clinical features (see below); (2) there is a close association between PTSD symptoms and pain symptoms after MVC, beginning soon after the collision, in those developing WAD (42,43); (3) like PTSD, chronic pain syndromes (such as fibromyalgia (44,45)) developing after MVC are characterized by stress system dysregulation; and (4) stress systems are capable of influencing pain processing (see below). Stress systems may contribute to pain development through multiple mechanisms, including via the initial stress response to the collision and associated injuries and via behavioral changes that occur after the collision.

Overlapping Clinical and Epidemiologic Features of WAD, PTSD, and Fibromyalgia

Fibromyalgia, PTSD, and WAD have overlapping clinical and epidemiologic characteristics. Female gender (1,15–17, 46,47), lower socioeconomic status (1,48,49), and a preexisting history of mood disorders (18,46,47,50) increase the risk of developing all 3 conditions. All are characterized by multisystem complaints, such as headache, axial pain, fatigue, cognitive dysfunction, and sleep disturbances (46,51,52).

PTSD commonly co-occurs with fibromyalgia and WAD. Clinically significant PTSD-like symptoms have been found in more than 50% of fibromyalgia patients (21,53) and in more than 50% of patients receiving treatment for chronic pain after MVC (54,55). At least 15% to 25% of patients with persistent whiplash symptoms meet diagnostic criteria for PTSD (56,57). Also, just as PTSD is common in patients with chronic pain, chronic pain is also common in patients with PTSD. Twenty percent to 30% of outpatient samples with PTSD (58–60) and 80% of combat veterans with PTSD (59) also have chronic pain. Recent epidemiologic studies have also established genetic linkage between fibromyalgia, PTSD, and other "affective spectrum" disorders (61).

Sexual abuse is the most common cause of PTSD in women (62), and a history of previous trauma or child abuse increases the risk of developing PTSD after a traumatic event (38,63). Fibromyalgia populations report an increased prevalence of child abuse; 50% or more of tertiary care clinic populations report such a history (64–66). Child abuse can cause permanent stress system dysregulation (67), and such dysregulation may render abuse victims more vulnerable to subsequently developing fibromyalgia or WAD after MVC or other stressors. Recent animal studies have confirmed that early life stress can permanently alter nociceptive circuitry (68,69). The prevalence of self-reported child abuse among community-based samples of fibromyalgia patients who report the onset of chronic pain after MVC is unknown, as is the prevalence of child abuse among patients with WAD. The above data suggest the testable hypothesis that such prevalence rates are higher than those of the general population.

Association Between PTSD Symptoms and WAD Symptoms During WAD Development

Most studies examining the relationship between chronic pain and PTSD are cross-sectional and thus cannot provide information on the relative timing of pain and PTSD symptoms after MVC. Available evidence suggests that pain and PTSD symptoms are closely associated, beginning soon after MVC (42,43,70). In addition, PTSD symptoms after MVC have been shown to predict the development of chronic WAD. Drottning (43) found that increased PTSD symptoms within 1 to 2 days of the MVC were found in 70% of patients with significant neck pain 4 weeks after MVC as opposed to only 26% of those in the low pain group. Sterling et al. (42) found that elevated Impact of Event Scale scores (which reflect PTSD symptomatology) within 1 month of MVC were unique to those with moderate or severe WAD at 6 months. A recent study by Sterling et al. (71) also found that PTSD symptoms after MVC predicted whiplash severity at 6 months. These data suggest that evidence of vulnerability to PTSD in the immediate aftermath of a MVC predicts subsequent development of chronic WAD. Evidence that a subset of those with neck pain after MVC progresses to develop fibromyalgia (72) suggests that WAD and FM may be linked and that vulnerability to develop PTSD after MVC may also predict the development of fibromyalgia. These data suggest the testable hypothesis that factors which predict vulnerability to PTSD in prospective studies will also predict vulnerability to WAD and fibromyalgia.

Like PTSD, Fibromyalgia Developing After MVC Is Characterized by Stress System Dysregulation

A comprehensive review of the complex and heterogeneous literature regarding stress system findings in PTSD and fibromyalgia is beyond the scope of this review. However, abnormal stress system function is an important feature of both disorders (44,73). Though specifics have varied across studies and there have been conflicting findings, the preponderance of evidence suggests that the HPA axis is dysregulated in patients with PTSD (73,74). Both excessive and reduced HPA axis activity has been seen (74). Increased cerebrospinal fluid corticotrophin-releasing hormone (CRH), blunted ACTH responses to CRH, low baseline cortisol levels, and altered cortisol responses to acute stressors have all been reported (73,74) in PTSD. LC/NE system dysregulation is also present in PTSD, with a heightened catecholamine and autonomic response to stressors (75). Like PTSD, HPA axis findings in fibromyalgia have also been inconsistent, with both hyper- and hypoactivity noted (76). Also like PTSD, heightened autonomic reactivity (reflected in both heart rate variability and plasma catecholamine levels) has been observed in fibromyalgia and suggests a central hypernoradrenergic state (77,78).

Neuroanatomical work in PTSD suggests dysregulation in limbic, paralimbic, and prefrontal regions, many of which are involved in the stress response and emotional processing (79). Considerable interest has focused on prefrontal circuitry, which is responsible for the modulation of emotional responses, and amygdaloid regions, which are important in processing fear and emotional salience (79). An emerging hypothesis suggests that decreased prefrontal inhibition of amygdaloid and/or hypothalamic activity may contribute to altered HPA function, autonomic/adrenergic hyperactivity, and the generation of some PTSD symptoms (80). Intriguingly, abnormal prefrontal function has also been associated with pain catastrophization (81), which is associated with the development of chronic musculoskeletal pain (82). Future research is warranted to explore the possibility that prefrontal dysregulation, in some cases rooted in early life stress, may contribute to vulnerability to and manifestations of both PTSD and poststress pain syndromes by permissively contributing to the dysregulation of subcortical neuroendocrine, autonomic, emotional, and pain processing centers.

Stress Systems Are Capable of Influencing Pain Processing

In animal studies, prefrontal cortical regions are capable of influencing widespread pain sensitivity via their influence on descending pain modulatory pathways (83). These pathways can either inhibit or facilitate the spinal transmission of both noxious and nonnoxious stimuli (84) via opioid and nonopioid mechanisms (85). In addition, the laterocapsular division of the central nucleus of the amygdala also appears to play an important role in pain modulation (86). This area, which has been described as the "nociceptive amygdala," is capable of either enhancing or suppressing painful stimuli (86) and may be critical to the development of chronic pain after MVC in some patients.

The possible dysregulation of descending pain modulating pathways in poststress pain states is suggested by the early onset and widespread nature of the hyperalgesia, which develops soon after MVC (70,87) in some patients who develop chronic WAD (31). Patients with WAD have been found to have the same widespread hypersensitivity to sensory stimulation as patients with fibromyalgia (88), and considerable data in fibromyalgia suggest that antinociceptive pathways are hypoactive in this condition (89–93). Recently, evidence of abnormal function of antinociceptive pain pathways has been identified in individuals developing chronic WAD, beginning soon after the MVC (94).

Although contemporary evidence most strongly suggests that stress systems influence post-MVC pain development via descending pain modulatory pathways, stress systems are also capable of modulating pain via other mechanisms, such as via spinal cord dorsal horn glucocorticoid receptors. Such receptors respond to peripheral nociceptive stimulation (95,96) and are capable of inducing antinociception (97–99). Cortisol variation may also influence the balance of peripheral proinflammatory cytokines, which might contribute to pain symptoms via peripheral or central mechanisms (100).

CANDIDATE NEUROBIOLOGICAL PROCESSES INVOLVED IN THE RESOLUTION OR PERSISTENCE OF SYMPTOMS AFTER MVC

Given the linkages described above between trauma, stress, PTSD, fibromyalgia, and WAD, it seems logical to wonder whether the acute stress response factors that mark or create vulnerability to PTSD may also contribute to vulnerability to develop chronic pain. No studies have examined the importance of stress response systems and their acute reactivity in the development of chronic pain after MVC. We might hypothesize that heightened acute autonomic activity and variations in HPA axis activity after MVC would predict an increased likelihood of subsequently developing WAD and fibromyalgia.

Stress response system dysregulation after MVC would then interact with cognitive-behavioral factors, such as avoidance learning, to further modulate neurobiological systems related to pain processing and stress. Consistent with this hypothesis, recent studies indicate that cognitive-behavioral factors alter pain perception and other symptoms via central neurobiological pathways (81,101). Such evidence supports a model of chronic symptom development that incorporates the potential for interactions between past experience, acute stress responses to trauma, post-MVC behavior, and cognitive/psychosocial consequences to alter activity within pain-sensitive brain regions and affect pain, as well as other psychological experiences (Figure 2). This model also suggests that, in many individuals, the dysregulation of neurobiological processes related to stress systems in the early aftermath of trauma may be a critical step in chronic pain development. If posttraumatic pain syndromes are similar to PTSD in this regard, there may

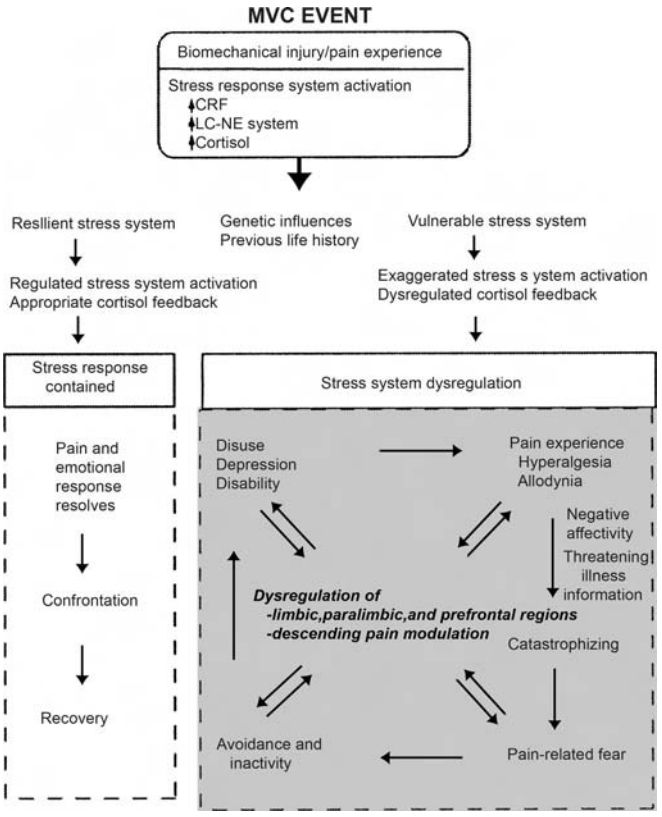

Figure 2. Amendment to Vlaeyen's cognitive-behavioral model of chronic pain pathogenesis, incorporating the hypothesized role of the stress response system in the development of aberrant pain and/or emotional processing after motor vehicle collision.

be value in testing the ability of agents like propranolol or hydrocortisone, delivered in the immediate aftermath of trauma, to prevent the development of chronic pain.

POSSIBLE NEUROBIOLOGICAL MECHANISMS MEDIATING KNOWN ENVIRONMENTAL RISK FACTORS FOR CHRONIC PAIN DEVELOPMENT

The utility of an interactive model incorporating neurobiological and cognitive-behavioral factors can be further illustrated by considering one post-event factor known to influence individual outcomes: decreased activity level. Decreased activity after MVC increases the risk of WAD (102), but the mechanisms by which decreased activity influences nociceptive processing are unknown. Results from a recent study suggest that depriving normally exercising individuals of routine exercise (as may occur if an individual reduces activity after MVC) may lead to symptoms such as pain, fatigue, and mood disturbances and that stress response system function may identify those individuals particularly vulnerable to the development of such symptoms (103). After 1 week of exercise cessation, 8 of 18 subjects developed worsening pain, tenderness, fatigue, or mood symptoms. These 8 subjects had significantly reduced baseline HPA axis activity (mean AM cortisol 27.42 μg/dl versus 37.97 μg/dl) and autonomic nervous system function (heart rate variability assessed using total power 7662 m/s^2 versus 13,929 m/s^2) relative to subjects who did not develop such symptoms.

These data support the hypothesis that stress system activity, shaped by genetic or experiential factors, predicts vulnerabilities to develop altered mood and pain experiences in the setting of reduced activity. This has relevance to the potential contribution of reduced activity following MVC to the development of chronic pain and suggests that reduced activity may also increase the risk of developing psychological sequelae. In addition, these data indicate that a full explanation of the link between decreased activity and chronic pain development may require a model that incorporates meaningful interactions between stress response systems, behavior, and central pain processing pathways.

These data also suggest a mechanism whereby interactions between central neurobiological pain processing systems and stress response systems may contribute to cultural variations in WAD prevalence via both MVC-related and post-MVC-related factors. There are cultural differences in the expected consequences of whiplash injury (104), and in those cultures in which more chronic sequelae are expected, the MCV event itself may be more likely to result in an exaggerated and/or poorly modulated stress response, which in vulnerable individuals may lead to persistent pain and/or psychological symptoms. In addition, individuals in countries where the perceived threat of MVC is high may also be more likely to decrease their activity level after an MVC (eg, "rest up" after the injury), which also may contribute to symptom development in vulnerable individuals via central neurobiological processes. These mechanisms are not mutually exclusive and in fact may often occur together and be synergistic.

CONCLUSIONS

In summary, a number of lines of evidence suggest that central neurobiological processes, such as those related to stress response systems and central pain processing, may be important to the development of persistent pain and psychological sequelae after MVC. We propose a model in which the acute physical and emotional effects of MVC involve an interaction between the direct effects of tissue injury and the emotional responses to the experienced threat. This emotional response to threat includes the response to the MVC itself, as well as the response to associated injuries and symptoms after the MVC. These physical and emotional effects interact with an acute stress response that has been shaped by genetics and prior traumatic experience. Together, these influences in turn interact with central processing pathways, including those related to pain, that are highly sensitive to cognitive and emotional modulatory input. Amplified pain signaling may result, which may then interact with post-MVC behaviors to produce further amplification and reverberating activity that becomes self-sustaining.

This model incorporates all of the relevant factors identified in prior biopsychosocial theories of chronic pain development after injury and places them in the landscape of our rapidly developing understanding of stress systems and CNS

pain-modulating pathways. It should be useful in shaping further studies of chronic symptom development after MVC, as it generates numerous specific, testable hypotheses. Longitudinal studies will be needed to test some of these hypotheses and to examine the influence of central factors in the development of chronic WAD, fibromyalgia, and PTSD among unselected patient cohorts. Examining these factors longitudinally will allow evaluation of the mechanisms that are likely to directly mediate chronic symptom development. Such studies should simultaneously examine a range of outcomes after MVC, including both regional and widespread pain and psychological sequelae. These studies will allow us to learn more about the rich and complex interactions between central neurobiological processes and psychosocial factors which occur during the transition from acute injury to chronic disorder, whether the outcome is a chronic pain disorder like WAD or fibromyalgia or a psychiatric disorder like PTSD. They may also lead us to acute, posttrauma interventions that may be able to prevent development of both PTSD and chronic pain syndromes.

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Biomedical models of fibromyalgia

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Abstract

Purpose. Fibromyalgia (FM) and chronic widespread pain (CWP) are common, but the etiology of these disorders remains poorly understood. A large body of data indicates a neurobiological basis for these disorders, but this information has not been effectively transmitted to many medical professionals.

Methods. Contemporary data on the epidemiologic characteristics of FM and CWP are reviewed, and evidence for a neurobiological basis for these disorders is presented. In addition, possible predisposing, triggering, and maintaining factors for the development of these disorders are discussed.

Results. Approximately 10% of the population have CWP, and approximately 4% have FM. The tender point criteria for FM have resulted in the common misconception among health care professionals that this spectrum of disorders is limited to women with high degrees of psychological distress. A hallmark of FM is the presence of non-nociceptive, central pain. There is evidence of centrally augmented pain processing, which can be detected both with sensory testing and by more objective measures (e.g., evoked potentials, functional neuroimaging).

Discussion. An appreciation of the neurobiological basis for these disorders, and an understanding of some of the abnormalities of pain processing present in patients with FM, will hopefully provide greater understanding of these patients. It may also serve to decrease the level of frustration and improve the care experience of both chronic pain patients and physicians.

Keywords: *Fibromyalgia, pain, neurobiology*

Introduction

Fibromyalgia (FM) is currently defined as the presence of both chronic widespread pain (CWP) and the finding of 11/18 tender points on examination. The etiology of these common disorders remains poorly understood. While there is a large body of evidence demonstrating a neurobiological basis for these disorders, this information has been poorly communicated to health care providers. The purpose of this review is to describe the epidemiologic characteristics of FM and CWP, and to summarize contemporary evidence regarding the neurobiology of these disorders. In addition, possible predisposing, triggering, and maintaining factors for the development of these disorders will be discussed.

Epidemiology of chronic widespread pain and fibromyalgia

Population-based studies of chronic widespread pain (CWP) in the US and UK suggest that approximately 10 – 11% of the population has this symptom at any given point in time [1,2]. Chronic regional pain is found in 20 – 25% of the population [1]. Both chronic widespread and regional pain occur about $1\frac{1}{2}$ times as commonly in women than men.

Influence of tender point criteria in fm

The 1990 American College of Rheumatology (ACR) criteria for FM require that an individual has both a history of CWP, and the finding of 11 of 18 possible tender points on examination [3]. Tender points are defined via nine paired regions of the body. If an

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individual reports pain when a region is palpated with 4kg of pressure, this is considered a positive tender point. Using this ACR criteria, the population prevalence of FM in industrialized countries has been reported to range from 0.5–4% [4,5].

The demographic and psychological characteristics of FM are strongly influenced by the tender point requirement in the ACR criteria. Women are only $1\frac{1}{2}$ times more likely than men to experience CWP, but are 11 times more likely than men to meet tender point criteria for FM [4,5]. Because of this, women are approximately ten times as likely to meet criteria for FM.

The presence of tender points is also associated with an increased level of distress. Wolfe has described tender points as a 'sedimentation rate for distress' [6]. Distress is typically operationalized as some combination of somatic symptoms and symptoms of anxiety and/or depression. Until recently, it was assumed that because tender *points* were associated with distress, tenderness (an individual's sensitivity to mechanical pressure) was associated with distress [7,8]. However, recent evidence suggests that this association is due instead to standard tender point assessment techniques, which consist of applying steadily increasing pressure to the patient during testing [9]. In this situation, individuals who are anxious or 'expectant' have a tendency to not want to experience pain from the subsequent tender point exams, and thus they state that they are having pain even before they really experience it as pressure is applied. Thus, the results can be strongly influenced by patient distress. Recently, more sophisticated measures of tenderness have been developed which give stimuli in a random, unpredictable fashion; the results of these tests are independent of psychological status [9].

In summary, although many clinicians associate FM with females who display high levels of distress, it should be appreciated that much of this is an artifact of the ACR criteria that require 11 tender points. This view of FM is also likely due to the fact that most studies of FM have originated from tertiary care centers, where healthcare seeking behaviors increase the prevalence of psychological and psychiatric co-morbidity in the clinic population [10]. The rate of current psychiatric co-morbidity in patients with FM may be as high as 30–60% in tertiary care settings, and the rate of lifetime psychiatric disorders even higher [11,12]. However, individuals who meet ACR criteria for FM who are identified in the general population do not have nearly this high a rate of identifiable psychiatric conditions [7,10].

Abandoning the requirement for 11/18 tender points from the FM criteria would lead to a disorder with markedly different characteristics: one affecting far more men, with considerably lower levels of average patient distress. In reality, the overall association between chronic widespread pain and distress is modest [7,13]. There are far more psychologically 'normal' individuals who develop CWP than distressed or depressed people that do, and most individuals with CWP do not develop distress or depression [14,15].

Association between the presence of cwp and other somatic symptoms

Many individuals with CWP also have other somatic symptoms, such as fatigue, memory difficulties, etc. This clustering of somatic symptoms in the population gives rise to overlapping syndromes such as fibromyalgia, chronic fatigue syndrome, multiple chemical sensitivity, somatoform disorders, etc [16]. (Figure 1) Population-based studies have been performed using factor analytic techniques, to identify the seminal features of these conditions [17]. The key symptoms that co-aggregate are multifocal pain, fatigue, memory difficulties, and mood disturbances [17].[7] The most common 'systemic' conditions in this spectrum are FM, Chronic Fatigue Syndrome, Multiple Chemical Sensitivity, and Gulf War illness, whereas the most common regional syndromes are irritable bowel syndrome, temporomandibular disorders, and migraine and tension headaches. Several studies have demonstrated that these conditions commonly present simultaneously in the same patient, and that individuals with one of these conditions are much more likely to have or develop another of these conditions [18].

The term Chronic Multi-symptom Illnesses has been coined by investigators from the US Centers for Disease Control and Prevention to describe this symptom complex [19,20]. Population-based studies of individual symptoms (e.g., pain, fatigue) suggest that the greater the number of co-aggregated symptoms, the more likely that the syndrome will be permanent, and the greater the likelihood that the individuals will seek medical care [21,22]. It should be noted that criteria for all of these disorders are arbitrary. In most cases, a group of experts took a symptom or finding that was continuously distributed across a wide range in the population (e.g., pain, fatigue, tenderness) and decided 'where to draw a line', such that on one side of the line individuals had the syndrome, and on the other side they did not.

Etiology of symptoms in FM

Neurobiology

The most consistently detected objective abnormalities in fibromyalgia involve pain processing systems.

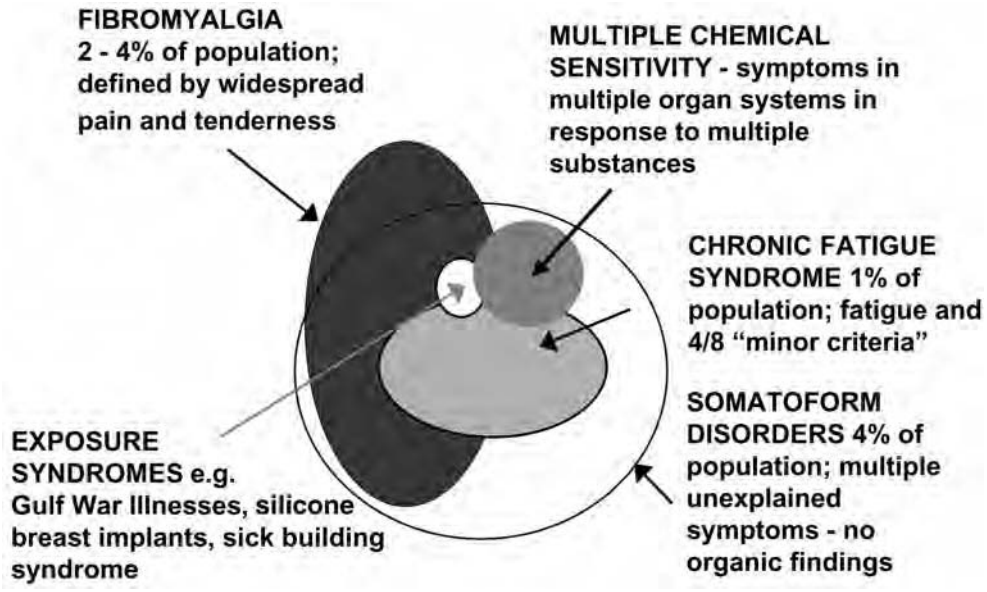

Figure 1. Examples of overlapping systemic syndromes characterized by otherwise unexplained chronic pain and fatigue.

Studies have demonstrated that FM patients cannot detect electrical, pressure, or thermal stimuli at lower levels than normal, but the point at which these stimuli are experienced as pain or unpleasantness is considerably lower [23,24]. Data corroborating the veracity of FM patients' pain complaints have been collected using paradigms that are not dependent on patients' subjective reports. For example, a recent study by Gracely and colleagues using functional magnetic resonance imaging demonstrated that the amount of pressure stimuli required to cause cerebral activation in pain processing regions of the brain (e.g., the primary and secondary somatosensory cortices) was much lower in FM patients than in healthy controls [25].

The increased tenderness in fibromyalgia is not confined to tender points, but instead extends throughout the entire body. Experimental pain testing studies have suggested that there may be a decrease in neural signals that descend from the brainstem, and normally inhibit the upward transmission of pain [26,27]. Other studies done using different techniques demonstrate that patients with FM exhibit altered temporal summation of pain stimuli administered as a thermal stimulus to skin or as a mechanical stimulus to muscle [28,29]. These latter studies suggest a parallel between the human condition of FM and the 'wind-up' phenomenon that leads to hyperalgesia and allodynia that has been extensively studied in animal models [30].

Biochemical studies performed on patient samples support the notion that there are central changes in pain processing in FM. These changes may be due to either high levels of pro-nociceptive peptides, or low levels of antinociceptive peptides. For example, several studies have shown that patients with FM have approximately threefold higher concentrations of Substance P in CSF than normal controls [31–34]. Other chronic pain syndromes, such as osteoarthritis of the hip and chronic low back pain, are also associated with elevated Substance P levels [35]. Once elevated, Substance P levels do not appear to change dramatically and do not become elevated in response to acute painful stimuli. Thus, high Substance P levels appear to be a biological marker for the presence of chronic pain.

Other studies have shown that the principal metabolite of norepinephrine, 3-methoxy-4-hydroxyphenethylene (MPHG), is lower in the CSF of FM patients [36]. This finding is important for two reasons. First, a reduction of norepinephrine-mediated descending, pain-inhibitory pathways that descend to the spinal cord may be a potential mechanism for causing the allodynia and hyperalgesia associated with FM. Second, some of the most effective drug therapies for FM provide augmentation of central adrenergic activity.

Serotonin levels may also be diminished in patients with this spectrum of disorders. Studies by Russell et al. [36] and Yunus et al. [37] have demonstrated reduced levels of serotonin and its precursor, L-tryphtophan, in the blood serum of patients with FM, as well as reduced levels of the principal metabolite 5-HIAA in the CSF. These findings suggest that defective serotonin synthesis or metabolism could be operative in at least some patients with FM.

One possible link between the systemic symptoms that these individuals experience, and the diffuse pain seen in this condition, is the sympathetic

nervous system. There is emerging evidence that FM may be characterized by a decrease in the activity of descending, anti-nociceptive pathways that begin in subcortical structures, including the locus ceruleus, and descend into the spinal cord. Under normal conditions, these pathways are tonically active, and inhibit the upward transmission of pain. Kosek and colleagues demonstrated that isometric contraction of muscle exerted the expected analgesic effect on pressure pain threshold in normal subjects, whereas FM patients responded to this maneuver with a paradoxically lowered pain threshold [38]. Other investigators studied the effect of a tonic painful stimulus on pain threshold in FM patients, and found that, in contrast to controls, there was no increase in pain threshold [39]. They suggested that this indicated a lack of descending noxious inhibitory control mechanisms in the FM patients.

The absence of these modulating influences on the transmission of pain represents one of many plausible ties between the diffuse pain seen in FM and related conditions, and the stress response system. The responses to many different types of stressors (infection, other immune stimuli, physical trauma, emotional stress, etc.) are fairly stereotypical. In most instances, all of these acute stressors activate both the corticotropin-releasing hormone (CRH) and locus ceruleus-norepinephrine/autonomic (sympathetic/LC-NE) nervous systems [40]. Disturbances in all of the components of this system have been identified in FM, in a manner that could directly and indirectly cause widespread effects on sensory processing, autonomic regulation, and neuroendocrine function [41,42]. However, no consistent HPA or autonomic abnormality can be found in the majority of patients with this spectrum of illness. It is plausible that alterations of these stress-response systems identify a population vulnerable to the development of FM. Alternatively, altered neuroendocrine axis activity could cause or occur as a consequence of some FM symptoms. It is likely that these neurobiological alterations are shared with other poorly understood somatic syndromes and psychiatric disorders that frequently co-occur with FM.

Predisposing factors

Research has indicated a familial component to the development of FM, since family members of patients already diagnosed display a higher risk for FM – as well as common overlapping conditions – than seen in the general population [18,43]. This co-aggregation of conditions, which include FM, CFS, migraine and mood disorders, was originally collectively termed *affective spectrum disorder* [43], and more recently *central sensitivity syndromes* [44] and chronic multisymptom illnesses. Some of this variation in genetic risk may be due to variations in the activity of the biological stress response, as well as in systems that process sensory information such as pain. Data collected from animal studies show there are inter- and intra-species differences for the 'set points' for these systems. Set points may then be permanently altered by repeated exposure to environmental stressors.

Exposure to significant stressors early in life may be particularly influential in determining the subsequent biological response to stress in animals, because of the plasticity of these systems. Studies in rodents have demonstrated that exposure to endotoxin, trauma, or separation in the neonatal period all lead to permanent changes in the subsequent biological response to stress, extending throughout the life of the animal [45,46]. This plasticity may be due to changes in the numbers of neurons, number of circuits, and/or increases or decreases in gene expression – leading to permanent changes in molecules that define the function of the system. The permanent influence of early stressors could explain the increased prevalence of childhood physical and sexual abuse among patients with FM and related conditions [47,48], although the retrospective nature of these studies is problematic.

Triggering factors

Environmental factors may play a prominent role in triggering the development of FM and related conditions. Environmental 'stressors' temporally associated with the development of FM include physical (and particularly skeletal) trauma, certain infections (e.g., Hepatitis C, Epstein Barr virus, parvovirus, Lyme disease), emotional stress, and other regional pain conditions or autoimmune disorders [43,49,50]. An excellent example of how illnesses such as FM might be triggered occurred in the setting of the deployment of troops to liberate Kuwait during the Gulf War in 1990 and 1991. The term 'Gulf War illnesses' is now commonly used to refer to a constellation of symptoms developed by some 5–15% of the 700,000 US troops deployed to the Persian Gulf in the early 1990s. The symptoms, which include headaches, muscle and joint pain, fatigue, memory disorders, and gastrointestinal (GI) distress [20,51] were seen in troops deployed from the United Kingdom as well [52]. The panels of experts who examined potential causes for these symptoms and syndromes found that the sickness could not be traced to any single environmental trigger, and noted the similarities between these individuals and those diagnosed with other syndromes such as FM.

The type of stress and the environment in which it occurs also have an impact on how the stress response is expressed. It has been noted that victims

of accidents experience a higher frequency of FM and myofascial pain than those who cause them, which is congruent with animal studies showing that that the strongest physiological responses are triggered by events that are accompanied by a lack of control or support, and thus viewed as inescapable or unavoidable [39,40,53]. In humans, daily 'hassles' and personally relevant stressors seem to be more capable of causing symptoms than major catastrophic events that do not personally impact on the individual [54,55].

Maintaining factors

Available evidence indicates that the post-event environment can have a significant influence on the development of chronic symptoms. Much of this literature comes from studies of the development of chronic pain and multisystem illness after motor vehicle collision (MVC). Societies where the risk of chronic illness after MVC is believed to be high (increased perceived threat) have a higher risk of chronic symptom development [56]. In addition, more liberal disability or compensation systems can serve as 'permissive environments' that may augment the development and maintenance of chronic pain occurring after trauma [57–59]. As far as the central nervous system effects of stress are concerned, perceived is real, and perceived contingencies emanating from the environment need to be recognized as salient stressors along with the triggering event(s).

These systems can increase distress in patients by having them continue to prove that they are ill, and by having patients defend the veracity of their subjective complaints to an industry that is criticized for its negative impact on rehabilitation of chronic pain conditions. Important but rarely utilized interventions in the early post-exposure period include those that are somewhat effective in established fibromyalgia, but would likely be even more effective if initiated earlier. These include cognitive behavioral approaches; aggressive activation and exercise programs, pharmacological therapy aimed at chronic rather than acute pain, and multimodal programs that combine these modalities.

Conclusion

Many healthcare providers express enormous frustration aimed specifically at FM patients, or the FM 'construct'. The most simplistic reason for this may be psychological distress on the part of patients, physicians, or both. Patients with FM, especially those that meet the current criteria and present for secondary or tertiary care, display higher average levels of distress than individuals with other rheumatic disorders. Previous unsatisfactory interactions with the healthcare system may increase the likelihood of an adversarial relationship between patient and physician. In addition, current pharmacologic therapies are often ineffective, and non-pharmalogic therapies require time to implement.

Distress on the part of physicians is also likely due to the fact that mechanisms underlying FM symptoms are poorly understood, and that available evidence indicating a neurobiological basis for the disorder has been poorly communicated to healthcare providers. An appreciation of the neurobiological basis for the disorder, and an understanding of some of the abnormalities of pain processing present in patients with FM, will hopefully provide greater understanding of these patients. It may also serve to decrease the level of frustration and improve the care experience of both patients and physicians.

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Review

Fibromyalgia After Motor Vehicle Collision: Evidence and Implications

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Objective: *Assess currently available evidence regarding the ability of a motor vehicle collision (MVC) to trigger the development of fibromyalgia (FM).*

Methods: *Consensus standards developed by the American College of Rheumatology Environmental Disease Study Group were used to assess the ability of an MVC to trigger FM.*

Results: *Increasing evidence suggests that FM and related disorders are characterized by abnormalities in central nervous system function related to sensory processing, autonomic regulation, and neuroendocrine function. MVC trauma appears capable of triggering FM, but generally not through direct biomechanical injury. Instead, the evidence suggests that MVC trauma can act as a "stressor," which in concert with other factors, such as an individual's biologic vulnerability, psychosocial factors, cultural factors, and so on, may result in the development of chronic widespread pain and other somatic symptoms. MVC trauma is only one of many stressors which can trigger such disorders, and the environment within which the stressor is experienced (biological and psychosocial) may largely determine whether there is an adverse physiologic result or not.*

Conclusions: *The evidence that MVC trauma may trigger FM meets established criteria for determining causality, and has a number of important implications, both for patient care, and for research into the pathophysiology and treatment of these disorders.*

Keywords Fibromyalgia; Motor Vehicle Collision; Causality

Fibromyalgia (FM) is the second most common rheumatologic disorder in several industrialized countries, affecting 2–4% of the population (Jacobsen et al., 1992; Wolfe et al., 1995). Prevalence of the disorder increases with age, and females are 4–8 times more likely to be affected than males (Raspe et al., 1993; Wolfe et al., 1995). Diagnostic criteria for FM include the presence of chronic widespread pain involving all four quadrants of the body (and the axial skeleton), and the presence of 11 of 18 "tender points" on examination (Wolfe et al., 1990).

The ability of physical trauma, such as a motor vehicle collision (MVC), to trigger the development of FM remains the subject of intense debate (Wolfe, 2000). On the one hand, there are a plethora of case reports and anecdotal accounts of individuals who have developed FM in close temporal association with an MVC (Wolfe, 1994; Mailis et al., 2000). On the other hand, several authors have raised legitimate arguments regarding the scientific veracity of this linkage, and have appropriately argued that prematurely accepting such an association could be more harmful than good, to both individual patients and society (Wolfe et al., 1995; Winfield, 1997).

In his landmark 1965 paper, AB Hill proposed nine criteria for use when assessing for a causal association between an exposure and outcome (Table I) (Hill, 1965). These criteria have served as the gold standard for evaluating causation in the medical literature since that time. However, while Hill listed the types of criteria to consider, he did not suggest a particular formula or method for their application:

> What I do not believe . . . is that we can usefully lay down some hard-and-fast rules of evidence that must be obeyed before we can accept cause and effect. None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non. What

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Table I Nine aspects of an association to be considered when assessing causation (Hill, 1965)

Strength of the association
Consistency of the association
Specificity of the association
Temporal relationship of the association
Dose-response between exposure and outcome
Biologic plausibility
Coherence with current understandings
Experiment (de-challenge)
Analogy to other known associations

> they can do, with greater or less strength, is to help us make up our minds on the fundamental question. (Hill, 1965, p. 299)

Since that time, the Food and Drug Administration, other regulatory agencies, academic investigators, and pharmaceutical companies have developed standardized assessment methodologies using Hill's criteria (Stephens, 1987). These standardized methods were created because of the "real world" need to have standardized methods for determining causation (e.g., Is there sufficient evidence from case reports and other data to determine that a drug causes a particular adverse event?). Recently, the American College of Rheumatology convened an Environmental Disease Study Group to develop consensus standards for the process of identifying rheumatologic diseases that result from environmental exposures (Miller et al., 2000). In developing their assessment criteria, the study group examined contemporary algorithms for determining causation, and used the relative prevalence of individual criteria currently in use to develop their own consensus criteria (Table II).

In addition to developing standard assessment criteria, the study group also recommended a four stage process of identifying and defining environmentally associated rheumatologic disorders (Miller et al., 2000). During stage 1, an association is proposed via case reports or case series. These case series data and other data would need to meet or exceed the threshold criteria for determining causation listed in Table II. If causation is suggested, then during stage 2 the association between the exposure and outcome is tested using epidemiologic, clinical, and laboratory studies. If evidence in stage 2 continues to support causation, then during stage 3 classification and other criteria are developed to define the disorder. During stage 4, knowledge of the association undergoes continued refinement based on evolving data. The study group recognized that, in reality, research activities may occur in several stages simultaneously. However, the stage system provides explicit consideration of the amount of evidence supporting an association, thus preventing the premature (or delayed) acceptance of a causal association relative to the weight of the evidence (Miller, 2000). Since their publication, these study group criteria have been utilized to evaluate the relationship between anti-tumor necrosis factor α therapy for inflammatory arthritides and demyelination events (Mohan, 2001), and have been cited by an number of authors evaluating the relationship between environmental factors and rheumatologic illness (e.g., Nietert & Silver, 2000; Bresnihan & Cunnane 2003).

Table II Criteria for determining causality proposed by the Environmental Disease Study Group of the American College of Rheumatology (Miller et al., 2000)[A]

Essential elements (both must be present)
Temporal Association
Lack of likely alternative explanations
Primary elements (at least 1 of 3)
Dechallenge
Rechallenge
Biologic plausibility
Secondary Elements (at least 1 of 3)
Analogy
Dose Responsiveness
Specificity

[A]To publish findings of a possible causal relationship between an environmental exposure and a clinical syndrome, both essential elements, at least 1 of 3 primary elements, and at least 1 of 3 secondary elements must be present.

The purpose of this review is assess the evidence for a causal association between MVC and FM using the criteria in Table II, integrating evidence that physical trauma may trigger the development of FM into a contemporary understanding of FM and its causes. Increasing evidence suggests that: 1) FM is one of many overlapping clinical syndromes, 2) These syndromes are capable of being "triggered" when an individual is exposed to one of a number of different "stressors," including physical trauma. The conclusions of these findings have important consequences for future research into the causes and prevention of FM and related syndromes.

FIBROMYALGIA AND OTHER "CENTRAL SENSITIVITY SYNDROMES"

Although FM can be considered a discrete disorder, this condition overlaps significantly with other "systemic" conditions such as chronic fatigue syndrome, multiple chemical sensitivity, and Gulf War Illnesses, as well as with regional syndromes such as irritable bowel syndrome, TMJ (or TMD) syndrome, and headaches (Goldenberg, 1991; Russo et al., 1994; Plesh et al., 1996). Thus, to completely appreciate the nature of FM, one must move outside the field of rheumatology and examine the larger body of data that has been collected on these associated syndromes and conditions.

The influence of genetic factors in the development of fibromyalgia is suggested by the fact that FM, and many of the other illnesses within this spectrum, exhibit familial aggregation (Clauw et al., 1997). Family members of patients with FM display not only a higher than expected frequency of FM, but also a higher frequency of conditions related to FM, including chronic fatigue syndrome, irritable bowel syndrome, migraine headaches, and mood disorders (Buskila et al., 1997; Sann et al., 1998). This group of inter-related systemic and regional syndromes has been termed "central sensitivity syndromes" by Yunus (2000).

Environmental exposures, other than physical trauma, have been shown to be temporally associated with the development of FM. In all of these instances, the symptoms of FM continue well after the "stressor" has abated. Examples include several types of chronic infections (e.g., parvovirus, Hepatitis C, Lyme disease), emotional distress (acute or chronic), endocrine disorders (e.g., hypothyroidism), and immune stimulation, as may occur in a variety of autoimmune disorders (Middleton et al., 1994; Clauw & Katz, 1995; Buskila et al., 1997). For reasons that are elaborated later, these will all be considered to be biological "stressors."

Better-controlled studies have been performed looking at potential triggers of the development of chronic fatigue syndrome and Gulf War illnesses. With respect to chronic fatigue syndrome, it appears as though this syndrome can be triggered by certain prolonged infections, such as acute mononucleosis, but not common upper respiratory infections (Buchwald et al., 1996; Ayres et al., 1998; White et al., 1998). As with the above-noted "triggers" of FM, it is important to emphasize that the chronic fatigue and pain remains well after the infection has cleared, and that the accumulated data collected on this condition do not support a chronic active infection as the cause for sustained symptoms. (Clauw & Chrousos, 1997).

The epidemic of "Gulf War Illness" that occurred in troops deployed to the Persian Gulf in 1990 and 1991 affords an excellent example of how illnesses such as FM and chronic fatigue syndrome may be triggered. In 1990 and 1991, the U.S. deployed approximately 700,000 troops to the Persian Gulf to liberate Kuwait from Iraqi occupation. Fortunately, there were relatively few combat-related injuries and diseases during this conflict, but up to 45% of deployed veterans (as compared to 15% of non-deployed veterans) developed a constellation of symptoms and syndromes including muscle and joint pain, fatigue, memory problems, headaches, and gastrointestinal complaints (Fukuda et al., 1999). This experience was not unique to U.S. troops; veterans of this conflict from the United Kingdom experienced a similar increase in this spectrum of illness (Unwin et al., 1999). Several expert panels have been convened to examine these illnesses. There is agreement that this is not a single illness, but rather a constellation of symptoms and syndromes very similar to that seen in FM and CFS (Nisenbaum et al., 1998; Doebbeling et al., 2000). Multiple epidemiologic studies have been performed to assess the likelihood that any single environmental exposure (e.g., biological weapons, chemical weapons, drugs, etc.) may have led to the development of this illness. To date, the only single exposure to emerge as a risk factor was the administration of multiple vaccinations during deployment (Hotopf et al., 2000).

This epidemic of illness prompted a review of the health of U.S. service returning from other conflicts. This review found that similar chronic pain and fatigue syndromes have been reported after nearly every war in which the U.S. has been engaged (Hyams et al., 1996). The overall experience with Gulf War illnesses has led many to conclude that individuals are exposed to a plethora of "stressors" during war, including infections and other types of immune stimulation (i.e., vaccination), drugs or chemicals, physical trauma, or emotional stress. As a result of these exposures, some develop a chronic multi-system illness with features of FM or CFS (Clauw, 1998).

MVC AND FIBROMYALGIA: WEIGHING THE EVIDENCE

As noted previously, the largest body of "data" linking the development of FM to trauma is in the form of several case reports and case series reports (e.g., Jacobsen & Bredkjaer, 1992; Waylonis & Perkins, 1994). To date, there is only a single case-control study directly examining the relationship between FM and MVC (Buskila et al., 1997). Buskila et al. found that 22% of the individuals with neck injury, and 2% of patients with leg injury, developed FM one year after MVC (Buskila et al., 1997). Evidence for a causal relationship between MVC and FM may be comprehensively evaluated using the criteria listed in Table II:

1. **Temporal association**. There is no disagreement regarding a close temporal association between an MVC and the development of FM. Typically, the progression from acute regional pain to more widespread pain and fatigue predictably occurs within weeks to several months (e.g., Wolfe, 1994; Mailis et al., 2000). If such a pattern is not seen in a given individual it is unlikely that the MVC had any role in leading to the development of FM.
2. **Lack of likely alternative explanations**. Opponents of the notion that MVC can cause FM cite two possible alternative explanations for symptom development: malingering and psychosocial factors. Although there are undoubtedly a few individuals who malinger in this setting, even the most ardent opponents of the post-traumatic FM construct concede that this plays a very small role (Gardner, 2000; Wolfe, 2000).

   In contrast, there are substantial data indicating that psychosocial factors play a significant role in determining who will progress from an acute pain condition to chronic pain (Gatchel et al., 1995; Turk & Okifuji, 1997). However, rather than constituting an "alternative mechanism," psychosocial factors are best understood as an component of a process of chronic symptom development in which biological, psychological, and social factors all play an important role (biopsychosocial model).
3. **Biological plausibility**. In the past two decades, we have learned a tremendous amount about the underlying mechanisms that are operative in chronic pain states in general and in FM in particular. In parallel, there have been marked advances in our understanding of the neurobiology of "stress." Some of these constructs will be briefly reviewed, to provide a substrate for better understanding how physical trauma may trigger the development of FM.

   With respect to chronic pain, it is becoming increasingly clear that "central" factors play a much larger role than "peripheral" factors. For example, clinical studies have shown

that for nearly any chronic pain condition, there is a weak relationship between the degree of damage or abnormality identified in the periphery (for example, by imaging studies), and the degree of pain or functional impairment that an individual is suffering (Hochberg et al., 1995; Clauw et al., 1999). Historically, whenever there was a discrepancy between what was seen in the periphery (e.g., on the radiograph or MRI) and the symptoms experienced by the patient, this was attributed to psychological and behavioral factors. However, multiple studies in different chronic pain states suggest that while psychological and behavioral factors often do account for some of the variance, a substantial amount of the variance still remains unexplained in predicting outcome measures, or in predicting the transition from acute to chronic pain (e.g., Radanov et al., 1995; Creamer & Hochberg, 1998).

As clinical investigators were struggling with this enigma of unexplained chronic pain, animal researchers were elucidating spinal and supraspinal mechanisms that play prominent roles in chronic pain states. Constructs such as peripheral and central sensitization, "wind-up," descending control of pain pathways, and stress-induced analgesia and hyperalgesia all were first established in animal models, and then shown to be operative in various chronic pain states (e.g., Park et al., 1995; Dirig & Yaksh, 1996; Price & McHaffie, 1998). More recently, functional neuroimaging studies have confirmed that there are differences in cortical pain processing between chronic pain patients and controls, supporting the notion of biological amplification (Baron, 1999; Derbyshire, 1999).

In FM, recent studies have examined the basis for widespread pain and tenderness in this condition. Such studies have demonstrated that FM patients can not detect electrical, pressure, or thermal stimuli at lower levels than normals, but the point at which these stimuli are experienced as pain or unpleasantness is lower (Arroyo & Cohen, 1993; Lautenbacher et al., 1994). Sorenson and colleagues examined the responsiveness of FM patients to morphine, lidocaine, and sub-anesthetic doses of ketamine (Sorensen et al., 1995). They found that most subjects responded to one or more of these substances, and that the rate of placebo response was low. They suggested that this demonstrates that spinal or supraspinal mechanisms are involved in pain maintenance in this condition, and that this may be due to heterogeneous processes.

Other modulating influences have been examined to elucidate the precise mechanism(s) involved in pain transmission. One possible link between the systemic symptoms that these individuals experience, and the diffuse pain seen in this condition, is the sympathetic nervous system. There is emerging evidence that FM may be characterized by a decrease in the activity of descending, anti-nociceptive pathways that begin in subcortical structures, including the locus ceruleus, and descend into the spinal cord. Under normal conditions, these pathways are tonically active, and inhibit the upward transmission of pain. Kosek and colleagues demonstrated that isometric contraction of muscle exerted the expected analgesic effect on pressure pain threshold in normal subjects, whereas FM patients responded to this maneuver with a paradoxically lowered pain threshold (Kosek et al., 1996). Other investigators studied the effect of a tonic painful stimulus on pain threshold in FM patients, and found that, in contrast to controls, there was no increase in pain threshold (Lautenbacher & Rollman, 1997). They suggested that this indicated a lack of descending noxious inhibitory control mechanisms in the FM patients.

The absence of these modulating influences on the transmission of pain represents one of many plausible ties between the diffuse pain seen in FM and related conditions, and the stress response system. The responses to many different types of stressors (infection, other immune stimuli, physical trauma, emotional stress, etc.) are fairly stereotypical. In most instances, all of these acute stressors activate both the corticotropin-releasing hormone (CRH) and locus ceruleus-norepinephrine/autonomic (sympathetic/LC-NE) nervous systems (Chrousos & Gold, 1992). Disturbances in all of the components of this system have been identified in FM, in a manner that could directly and indirectly cause widespread effects on sensory processing, autonomic regulation, and neuroendocrine function (Crofford & Demitrack, 1996; Pilemer et al., 1997; Clauw, 1998).

In addition, the "environment" within which stress occurs may be the most important determinant of physiologic consequences. Stressors perceived as inescapable or unavoidable, or which are accompanied by lack of predictability or social support, evoke the strongest adverse biological consequences (Romero et al., 1993; Viau et al., 1993). This could conceivably explain why victims of trauma, such as motor vehicle accidents, appear to have a higher rate of the development of FM and myofascial pain than those who are responsible for the accident.

Finally, within any species, there are genetic differences in the activity of the biological stress response, as well as in systems that process sensory information such as pain. The aggregate data collected from such studies suggests that individuals may be born with a certain "set point" for the functioning of such systems, and that subsequent environmental exposures may change that set point over the life of that organism. For example, early life stressors can have a permanent and profound impact on the subsequent biological response to stress in animals, because of the plasticity of these systems (similar to the plasticity seen in pain processing systems).

Studies in rodents have demonstrated that exposure to endotoxin, trauma, or separation in the neonatal period all lead to permanent changes in the subsequent biological response to stress, extending throughout the life of the animal (Viau et al., 1993; Sapolsky, 1996). This plasticity may be due to changes in the numbers of neurons, number of circuits, and/or increases or decreases in gene expression—leading to permanent changes in molecules that define the function of the

system. This permanent effect of early stressors could explain the association often reported between individuals who develop FM and related conditions and a higher incidence of early life physical and sexual abuse (e.g., Goldberg et al., 1999; Finestone et al., 2000).

To summarize, there are abundant data suggesting that it is biologically plausible that physical trauma, acting as a stressor, could lead to the development of chronic widespread pain, as well as a number of other somatic symptoms. Particularly important constructs in this regard are that many different types of stressors are capable of eliciting similar responses, single exposures to stress can have chronic consequences, and that the environment within which the stressor is experienced may largely determine whether there is an adverse physiologic effect or not. These advances in the biology of stress and pain render dualistic arguments of biology versus psychology largely irrelevant.

4. **De-challenge**. For some environmentally associated rheumatic disorders (e.g., drug-induced lupus) removal of the offending agent leads to resolution of symptoms, strengthening support for a cause-and-effect relationship in this illness. To date, there is little evidence supporting a similar relationship in the case of trauma and FM.
5. **Re-challenge**. Patients who experience a second MVC have significant worsening of regional pain (Kan et al., 2000), and there is anecdotal evidence that FM symptoms worsen after repeat exposure to trauma.
6. **Analogy; are there previous reports of a similar disorder developing after the exposure in question?** Yes; as previously noted, there are abundant case reports and case series documenting that FM can develop after trauma of various types.
7. **Dose responsiveness**. There is no good evidence of dose responsiveness, if the intensity of trauma, rather than the response to trauma, is considered the "dose." In fact, the physical intensity of trauma appears to be relatively unimportant in determining who will develop acute or chronic pain after injury (Satoh et al., 1997; Kasch et al., 2001; Mayou & Bryant, 2001). For example, in a study of symptoms after an experimental sham MVC, 20% of patients reported neck pain three days after the event, despite the fact that no actual collision occurred (Castro et al., 2001). In contrast, the emotional distress surrounding the trauma, and the personal (Olsson et al., 2002), financial (Cassidy et al., 2000), and cultural (Ferrari & Russell, 1999) environment in which the trauma occurs, appear to be important factors.
8. **Specificity; are the defining symptoms, signs, and laboratory features of the disorder unique**. FM that occurs after trauma does not have any features that are reliably different from FM that occurs in other settings or under different circumstances. Thus, trauma may be only one of many types of stressors capable of producing symptoms characteristic of FM.

Using these above attribution elements, the association between FM and MVC meets criteria one (temporal association), two (lack of alternative explanations), three (biological plausibility), six (analogy), and possibly five (re-challenge). This meets or exceeds the recommended threshold for suspecting a causal relationship between an exposure and subsequent illness (stage 1 criteria). To put the relationship between FM and trauma in context, there are at least as much data supporting this relationship as there are for many other accepted environmentally associated rheumatic diseases.

IMPLICATIONS

To move forward from this point, further case-control or other population-based designs are necessary to more firmly establish causation, and to better understand the precise mechanisms that are operative. Such research could identify patients at high risk of developing FM after physical trauma and other stressors, identify important biological and psychosocial factors involved in the development of FM, and develop secondary prevention strategies.

Available evidence indicates that the post-event environment can have a significant influence on the development of chronic symptoms after a traumatic event. Societies where the risk of chronic illness after MVC is believed to be high (increased perceived threat) have a higher risk of chronic symptom development (Ferrari & Russell, 1999). In addition, more liberal disability or compensation systems can serve as "permissive environments" that may augment the development and maintenance of chronic pain occurring after trauma (Bellamy, 1997; Rainville et al., 1997; Miller & Topliss, 1998). As far as the central nervous system effects of stress are concerned, perceived is real, and perceived contingencies emanating from the environment need to be recognized as salient stressors along with the trauma. These systems can increase distress in patients by having them continue to prove that they are ill, and by having patients defend the veracity of their subjective complaints to an industry that is criticized for its negative impact on rehabilitation of chronic pain conditions.

We can and should educate our patients who are contemplating litigation or compensation for post-traumatic fibromyalgia. In particular, we should explore what they hope to gain from such an endeavor, and warn them of what is likely to happen. We should tell them that by pursuing such action they will rarely feel as though they have received "justice" in the legal system, and that it is even less likely that they will reap any financial reward. Even more importantly, they should be informed that numerous studies suggest that they are less likely to improve, and more likely to end up permanently on disability, if they follow this path (Littlejohn, 1989; Aaron et al., 1997; Cohen & Quintner, 1998).

The biggest opportunity we have as physicians is to prevent post-traumatic fibromyalgia. By the time that this is an appropriate label for the patient, chronicity may be a foregone conclusion. Patients with these types of injuries are frequently cared for by orthopedists or primary care physicians, many of whom are ill

equipped to manage this type of problem. Neck immobilization, inactivity, and time off work after MVC should be discouraged, as these factors have been shown to increase the risk of developing chronic pain (Borchgrevink et al., 1998; Rosenfeld et al., 2000).

There is probably a critical "window of opportunity" where individuals at risk of making the transition to fibromyalgia could be identified and given more aggressive management. Unfortunately, at present, the patient with unresolved acute pain is likely to receive more imaging studies (that frequently detect subtle abnormalities of questionable significance, but that reinforce the permanency of the injury), procedures of unclear efficacy, and/or aggressive physical therapy (which may encourage a passive, helpless approach on the part of the patient). More appropriate, but rarely utilized, interventions at this point are those that are somewhat effective in established fibromyalgia, but would likely be even more effective if initiated earlier. These include cognitive behavioral approaches, aggressive activation and exercise programs, pharmacological therapy aimed at chronic rather than acute pain, or multimodal programs that combine these modalities.

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Momentary Relationship Between Cortisol Secretion and Symptoms in Patients With Fibromyalgia

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Objective. **To compare the momentary association between salivary cortisol levels and pain, fatigue, and stress symptoms in patients with fibromyalgia (FM), and to compare diurnal cycles of cortisol secretion in patients with FM and healthy control subjects in a naturalistic environment.**

Methods. **Twenty-eight patients with FM and 27 healthy control subjects completed assessments on salivary cortisol levels and pain, fatigue, and stress symptoms, 5 times a day for 2 consecutive days, while engaging in usual daily activities. Only those participants who adhered to the protocol (assessed via activity monitor) were included in the final analyses.**

Results. **Twenty FM patients and 16 healthy control subjects adhered to the protocol. There were no significant differences in cortisol levels or diurnal cortisol variation between FM patients and healthy controls. Among women with FM, a strong relationship between cortisol level and current pain symptoms was observed at the waking time point ($t = 3.35$, $P = 0.008$) and 1 hour after waking ($t = 2.97$, $P = 0.011$), but not at the later 3 time points. This association was not due to differences in age, number of symptoms of depression, or self-reported history of physical or sexual abuse. Cortisol levels alone explained 38% and 14% of the variation in pain at the waking and 1 hour time points, respectively. No relationship was observed between cortisol level and fatigue or stress symptoms at any of the 5 time points.**

Conclusion. **Among women with FM, pain symptoms early in the day are associated with variations in function of the hypothalamic–pituitary–adrenal axis.**

Fibromyalgia (FM) is a common clinical syndrome defined by the presence of chronic widespread pain and tenderness (1). Recent studies have identified altered central nervous system (CNS) pain processing in individuals with FM, suggesting a neurobiologic basis for the disorder (2,3). However, the precise pathophysiologic mechanisms responsible for FM remain poorly understood.

The hypothalamic–pituitary–adrenal (HPA) system is the primary endocrine stress axis in humans and has been implicated in the pathophysiologic development of FM. The function of the HPA axis in patients with FM has been extensively examined, but study findings have been inconsistent. The majority of studies have identified abnormalities consistent with chronic

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hyperactivity of the HPA axis, including elevated cortisol levels (4–8) and a blunted response to acute stressors (5,8–11).

Most previous studies of the function of the HPA axis in FM have maximized internal validity by assessing patients in highly controlled, inpatient environments and by excluding FM patients with comorbid depression. A limitation of this approach is that the generalizability of the HPA axis findings from these studies to unselected FM populations (30–50% of whom have active depression [12–14]) is unclear. In addition, few studies have examined the relationship of HPA axis function to FM symptoms. Catley et al (6) performed the only previous study that examined cortisol levels and symptoms among FM patients and controls in a naturalistic setting. They found elevated salivary cortisol levels in FM patients that were not accounted for by differences in self-reported psychological stress, sleep quality, or demographic or psychosocial factors (6). No association was observed between cortisol level and patients' stress symptoms (6).

In their study, Catley et al (6) focused on the relationship of cortisol to psychosocial stress and did not examine the relationship between salivary cortisol levels and pain and fatigue symptoms in FM. Such a relationship would be indicative of the important immediate influence of cortisol on other, recently identified aspects of CNS function, such as emotional processing and memory. Among healthy controls, momentary cortisol levels have been associated with negative mood, anxiety, fear, and avoidant responses (15–19).

In this study we examined cortisol secretion in FM patients and healthy controls in a naturalistic setting, and included FM patients with severe symptoms of depression. In addition, we examined the momentary relationship between salivary cortisol level and concurrent pain, fatigue, and stress symptoms among women with FM. We hypothesized that there would be differences in cortisol secretion between patients and controls, and that salivary cortisol levels would be associated with current FM pain and fatigue symptoms. We also hypothesized that no momentary association would be identified between cortisol level and patients' stress symptoms, given the lack of relationship between cortisol level and stress symptoms in the study by Catley et al (6). In addition, because of increasing recognition of the important influence of self-reported physical or sexual abuse on the function of the HPA axis in adults (20,21), cortisol patterns were compared between women with FM and a history of abuse and those without a history of abuse, and abuse history was included as a covariate in regression model analyses.

PATIENTS AND METHODS

Participants. Participants comprised 2 groups: 28 patients with FM (of whom 22 were women; mean ± SD age 43 ± 9 years, 16 white [57%], 7 African American [25%], and 5 other race [18%]) and 27 healthy control subjects (of whom 12 were women; mean ± SD age 38 ± 9 years, 13 white [48%], 11 African American [41%], and 3 other race [11%]). There were significantly more women in the FM group.

Patients with FM and control participants were recruited via local print advertisements, and patients with FM were also recruited from local clinic samples. All participants received an initial specialized evaluation to determine if they met the American College of Rheumatology (ACR) 1990 criteria for the classification of FM (1). Patients who reported a history of FM but did not meet the ACR criteria at the time of the study were excluded. The presence of psychiatric disorders was assessed using the Composite International Diagnostic Interview (22). In addition, participants were asked if they had ever been the victim of physical or sexual abuse. No specific definition of physical or sexual abuse was provided. If a participant did report abuse, they were asked to report the age at which the physical or sexual abuse occurred or began.

To exclude other medical conditions, all participants underwent a detailed evaluation, comprising a medical history review, physical examination, and laboratory studies, which included determination of the complete blood cell count, levels of serum electrolytes, blood urea nitrogen, creatinine, and thyroid-stimulating hormone, the erythrocyte sedimentation rate, and C-reactive protein concentration. General exclusion criteria were 1) cigarette smoking, 2) substance abuse in the past 2 years, 3) medical conditions known to cause symptoms similar to those of FM, including obesity (body mass index >30 kg/m^2), autoimmune or inflammatory diseases, cardiopulmonary disorders, chronic asthma, uncontrolled endocrine or allergic disorders (e.g., hypothyroidism, diabetes, allergic rhinitis), or malignancy, or 4) schizophrenia or major depression with suicidal ideation. All participants were required to discontinue taking psychoactive medications at least 2 weeks prior to the study (4 weeks for longer-acting compounds such as fluoxetine). Menstruating women were scheduled to undergo study evaluations during days 3–7 of the follicular phase of their menstrual cycle.

Self-report instruments. Participants completed the following self-report instruments, each of which was chosen based on its psychometric properties and applicability to the FM population.

Center for Epidemiologic Studies Depression Scale (CES-D) (23). The CES-D is a 20-item measure that assesses multiple components of depression symptoms: depressed mood, feelings of guilt and worthlessness, feelings of helplessness and hopelessness, loss of appetite, sleep disturbance, and psychomotor retardation. The CES-D has demonstrated strong associations with other measures of depression symptoms (23) and has been validated in pain populations (24,25).

State-Trait Personality Inventory (STPI) (26). The STPI Form Y includes assessment of anger and anxiety symptoms.

This measure possesses strong psychometric properties for the assessment of these mood symptoms. The items have been well validated as parts of larger instruments such as the State-Trait Anxiety Inventory and the State-Trait Anger Inventory (27).

Short Form 36 (SF-36) health survey (28). The SF-36 includes 1 multi-item scale that assesses 8 health concepts: 1) limitations in physical activities because of health problems, 2) limitations in social activities because of physical or emotional problems, 3) limitations in usual role activities because of physical health problems, 4) bodily pain, 5) general mental health (psychological distress and well-being), 6) limitations in usual role activities because of emotional problems, 7) vitality (energy and fatigue), and 8) general health perceptions.

Procedure. Following the initial evaluation, participants completed assessments of ambulatory symptoms and salivary cortisol levels for 2 consecutive days at the following 5 time points: 1) upon awakening and prior to getting out of bed, 2) 1 hour after awakening, 3) 5 hours after awakening, 4) late afternoon between 3:00 and 4:00 PM, and 5) 30 minutes before going to bed. At each time point, participants were instructed to rate their pain, fatigue, and stress symptoms during the previous 30 minutes on a 10-point Likert scale, using an electronic storage device. No specific definitions of pain, fatigue, or stress were provided. Real-time assessments of ambulatory symptoms were performed because such assessments are not influenced by recall biases and are superior to retrospective symptom reports in many settings (29,30).

Symptom ratings at each time point were recorded using an electronic keypad placed on an ambulatory activity monitor (Actiwatch-Score; Mini Mitter, Bend, OR). The activity monitor is a wristwatch-size (37 × 29 × 9 mm), lightweight (17 grams) device with data entry and alarm-prompt capability that has been previously validated (31,32). Symptom ratings were made using the electronic keypad to improve compliance; activity patterns were used for validation of wake-up time assessments (33,34). To optimize participants' compliance with symptom recording and salivary cortisol determinations during daily activities, the monitors provided patients with 3 alerts (1 hour, 5 hours, and 9 hours after waking) that were preset based on each participant's self-reported usual wake-up time. The first and last entries were not accompanied by an alert, in order to minimize interference with participants' usual sleep–wake patterns. Care was taken for proper placement of the actigraph using a standardized mounting and positioning protocol (31).

Participants were also instructed to collect a salivary cortisol sample at each time point, after entering their symptom data. Salivary cortisol levels are reliable correlates of serum/plasma-free cortisol concentrations, and can be obtained with minimal interference with daily activities (35,36). Participants were instructed to refrain from eating and drinking for 30 minutes prior to obtaining a saliva specimen, and to collect their salivary samples before brushing their teeth (e.g., in the morning and evening). Participants chewed on a cotton swab for 45–60 seconds and then placed the swab in a special plastic tube (Salivette; Sarstadt, Newton, NC). Participants were asked to store the tube in their refrigerator prior to returning the samples to the research team on the day after protocol completion.

After the specimens were received from the study participants, the cotton swabs were centrifuged and saliva was divided into aliquots and deposited in a collecting vial, which was then topped, labeled, and frozen at −70°C until shipped for analysis. Salivary cortisol levels were determined by enzyme immunoassay (Salimetrics High Sensitivity Cortisol Kit; Salimetrics, State College, PA). All saliva samples were analyzed at the Michigan Diabetes Research and Training Center at the University of Michigan, and were run in a single batch to maximize reliability.

Quality control procedure for ambulatory data. Given the often-poor adherence of participants to research protocols in naturalistic settings (32), data quality was carefully assessed and data that appeared to be of poor quality were excluded. For each day of data, the time that the participant entered self-reported wake-up values into the electronic keypad was compared with actual wake-up time (estimated via activity monitor [31,32]). If the difference between these 2 times exceeded 30 minutes, data from that day were excluded from the data analyses. The average amount of sleep per night (in minutes) was also calculated using actigraphy data from the 2-day period.

Assessment of ambulatory sleep parameters. Actigraphy data were used to assess the duration of sleep, restlessness during sleep, and sleep efficiency of study participants, as described previously (37). Wake-up time and sleep time were based on patients' self reports and were validated using actigraphy data. Based on prior validation studies, patients were deemed awake when activity exceeded 50% of the average daytime activity level, and asleep when activity levels reached 50% below patients' average nocturnal level. Average nocturnal activity levels were assessed for each of the 2 nights prior to salivary cortisol assessment. The sleep fragmentation index was also used as a second, actigraph software–based indicator of restless sleep, and was calculated as follows: (% 1-minute intervals of movement during sleep + % 1-minute intervals of immobility) divided by total 1-minute immobility intervals (determined by actigraphy). Sleep latency was defined as the time between going to bed and actual sleep start, which was determined as the first 10-minute span of immobility (<40 counts per minute). Sleep efficiency, used as a measure of sleep quality, was defined as follows: (time in bed spent asleep divided by total time in bed) multiplied by 100.

Statistical analysis. The data were evaluated for the presence of outliers via box plots, and salivary cortisol variability at each time point was assessed using coefficients of variation. The Wilcoxon–Mann-Whitney test was used to compare continuous variables, and Fisher's exact test was used to compare categorical variables between the FM and control groups. Differences in cortisol patterns between FM and control participants were evaluated via repeated-measures analysis of variance. In addition, among women with FM, unadjusted morning (defined as AM hours) cortisol values and diurnal variation of cortisol between those reporting and those not reporting a history of physical or sexual abuse were compared using Spearman's rank correlation.

Among women with FM, the momentary association between cortisol level and pain, fatigue, and stress symptoms at each time point was evaluated using a linear regression model with repeated measures, with unstructured variance–covariance within subjects across days. This regression model was also used to assess the association between sleep quality measures and morning cortisol and symptom levels. In addi-

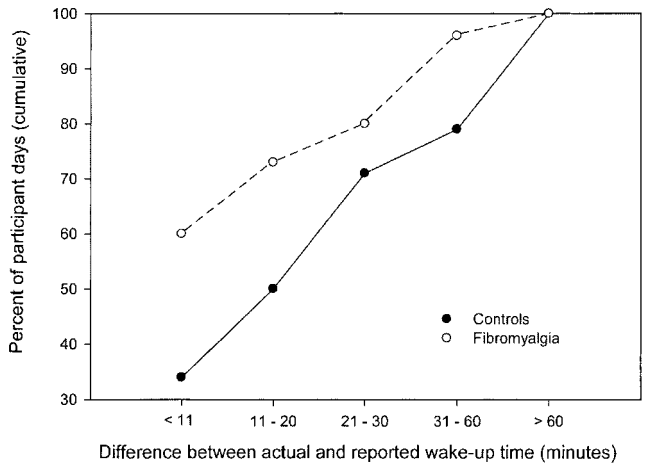

Figure 1. Difference between self-reported wake-up time and actual wake-up time estimated by actigraphy, as a percentage of cumulative participant-days, among patients with fibromyalgia and healthy controls.

tion, the association between wake-up time and cortisol level at wake-up was also evaluated. Age, amount of depression symptoms, and abuse history were included as covariates in each model. All regression models were evaluated for normality, and goodness-of-fit and model aptness were evaluated using residual analysis.

The amount of variance in pain symptoms at each time point accounted for by cortisol level alone was calculated using a coefficient of determination. In addition, for each woman with FM, the association between cortisol level and pain symptoms was calculated by Pearson's correlation coefficient, and a correlation between this value and patients' symptom characteristics was assessed using Spearman's rank correlation. Statistical analyses were performed using SPSS software (SPSS, Chicago, IL).

RESULTS

Data quality assessment. One hundred ten participant-days of data were collected. Ten morning cortisol values were missing, leaving 100 cortisol values at the wake-up time point. Of these 100 values, both self-reported and actigraphy-determined wake-up data were available for 83 participant-days. On 20 (24%) of these days, the difference between the self-reported wake-up time and actual wake-up time was more than 30 minutes. (See Figure 1 for differences between actual and reported wake-up times among FM and control participants.) Due to the questionable nature of this difference, the data from these days were excluded, resulting in the exclusion from the final data set of 8 (29%) of 28 patients with FM and 11 (41%) of 27 control participants. The remaining data, from 20 patients with FM and 16 controls, were used in subsequent analyses.

Of the 360 possible data entry points (36 participants × 2 days × 5 signals per day) for each parameter (cortisol level, pain score, fatigue score, and stress score), participants provided 329 salivary cortisol samples (91.4%), 353 pain scores (98.1%), 344 fatigue scores (95.6%), and 329 stress scores (91.4%). Because differences in the missing cortisol data between the FM patients and control participants could bias the analyses, we examined the overall rate of missing data and the pattern of missing data over the day by group. A generalized linear model analysis indicated that there were no group differences in the rate ($Z = -0.77$, $P = 0.44$) or pattern ($Z = 0.43$, $P = 0.67$) of missing cortisol data, thus allowing the inclusion of random missingness.

Preparation of cortisol data. There were no marked individual outliers, and therefore all values were included in the analyses. The cortisol data exhibited high variability. The coefficients of variation for the 5 salivary cortisol assessment times were 51.53%, 50.24%, 43.72%, 49.74%, and 66.96%.

Participants' symptoms and characteristics. Participants with FM had markedly higher levels of pain, fatigue, stress, and symptoms of depression than did control participants (Table 1). There was a greater

Table 1. Characteristics of the study participants*

Characteristic	Controls (n = 16)	Patients with FM (n = 20)
Age, mean ± SD years	39 ± 9	43 ± 9
BMI, mean ± SD kg/m^2	25 ± 3	26 ± 4
Male, no. (%)	12 (75)	4 (20)†
Race, no. (%)		
White	8 (50)	10 (50)
African American	7 (43)	6 (30)
Hispanic	0	3 (15)
Other	1 (6)	1 (5)
Symptom score, mean ± SD		
Ambulatory pain	1.1 ± 0.2	4.8 ± 1.8‡
Ambulatory fatigue	1.8 ± 0.9	4.7 ± 2.0‡
Ambulatory stress	1.5 ± 0.9	3.2 ± 2.0†
CES-D	4.4 ± 5.8	17.5 ± 8.6‡
Sleep characteristics, mean ± SEM§		
Duration, hours	7.0 ± 0.5	6.8 ± 0.4
Sleep latency, minutes	11.7 ± 6.4	16.0 ± 5.3
Average nocturnal activity level	106.8 ± 18.9	118.8 ± 15.8
Sleep fragmentation index	10.0 ± 3.1	15.5 ± 2.6
Sleep efficiency level	84.9 ± 2.6	85.3 ± 2.2
Actigraphy wake-up time, mean ± SD time, AM§	07:15 ± 1:31	06:17 ± 1:14

* FM = fibromyalgia; BMI = body mass index; CES-D = Center for Epidemiologic Studies Depression Scale.
† $P < 0.01$ versus controls.
‡ $P < 0.0001$ versus controls.
§ Adjusted for age and sex.

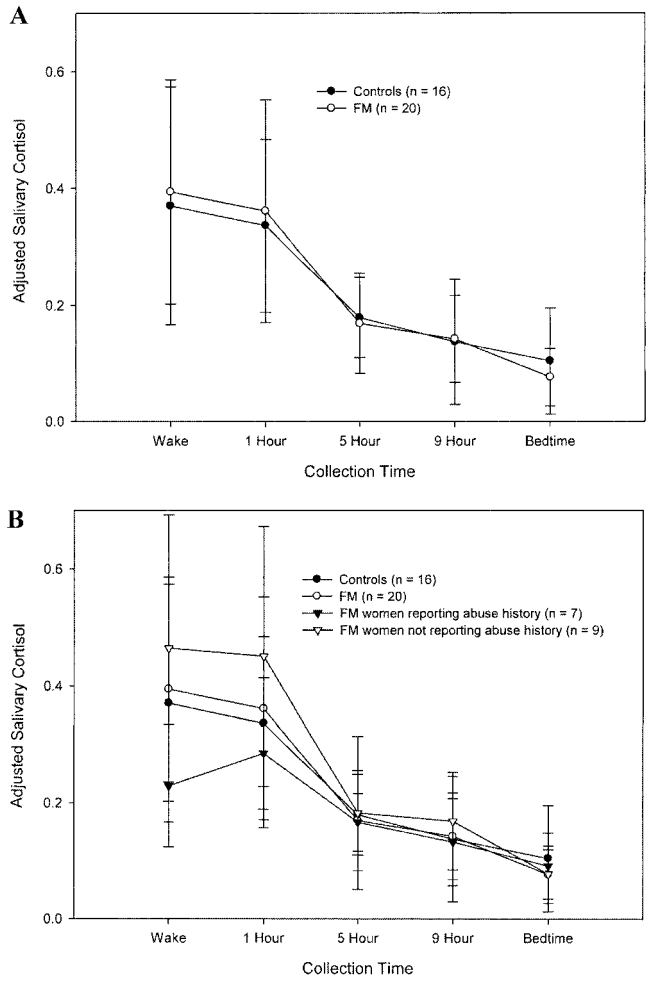

Figure 2. Salivary cortisol values (in μg/dl), adjusted for age and sex, across the 4 time points among patients with fibromyalgia (FM) and healthy controls **(A)**, and among women with FM reporting and those not reporting a history of abuse **(B)**. Bars show the mean ± SD.

number of women in the FM group. Consistent with prior observations (38), chronic fatigue syndrome, as defined by the Centers for Disease Control and Prevention criteria (39), often coincided with FM in the patients (16 of 20 patients, or 80%). Ten of the 20 participants with FM had significantly increased ratings of depression symptoms (CES-D score ≥16), compared with only 1 of the 16 control participants. Participants with FM had a longer sleep latency, more restless sleep (higher average nocturnal activity level and sleep fragmentation index), and an earlier wake-up time than did controls.

Adjusted group differences in salivary cortisol levels. Plots of adjusted salivary cortisol values by group at each time point, adjusted for age and sex, are shown in Figure 2A. In repeated-measures analysis, time-of-day and group effects were not significantly different between patients with FM and control participants.

Association between self-reported history of physical or sexual abuse and salivary cortisol secretion among women with FM. Of the 16 women in the FM group, 7 (44%) reported a history of physical or sexual abuse. Four reported a history of abuse during the preteen years (ages 6–13 years), 2 reported a history of abuse as young adults, and 1 participant did not provide information regarding the time period of abuse. One of the women with a history of abuse met the diagnostic criteria for posttraumatic stress disorder. None of the men with FM and none of the control participants reported a history of abuse. There was no significant difference in the mean number of depression symptoms among the women with FM when comparing those with and those without a self-reported history of abuse (mean ± SD 20.5 ± 7.7 versus 17.3 ± 10.2; $P = 0.33$).

Among the women with FM, those reporting a history of physical or sexual abuse had a lower unadjusted morning cortisol level (mean ± SD 0.23 ± 0.11 μg/dl versus 0.46 ± 0.23 μg/dl; $P = 0.028$) and decreased diurnal cortisol variation (0.13 ± 0.12 μg/dl versus 0.39 ± 0.21 μg/dl; $P = 0.011$) than those without a history of abuse. There was no difference in mean wake-up time between those reporting a history of abuse (mean ± SD 6:07 ± 1:23 AM) and those not reporting a history of abuse (6:41 ± 1:29 AM) ($t = 1.32$, $P = 0.20$). Although the group numbers were too small to allow meaningful repeated-measures analysis, mean cortisol values at individual time points suggest that diurnal

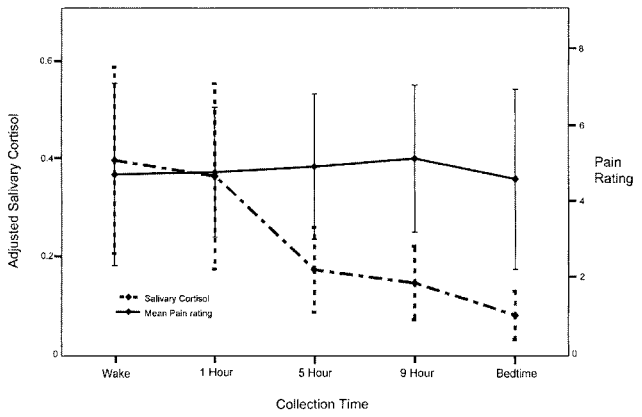

Figure 3. Ambulatory salivary cortisol values (in μg/dl) versus ambulatory pain ratings (on a 10-point Likert scale), adjusted for age, sex, and abuse history, among patients with FM. Bars show the mean ± SD.

Table 2. Linear regression models examining the momentary relationship of cortisol level to pain symptoms among women with fibromyalgia (n = 16)

Dependent measure, independent variable*	Beta	*t*	*P*
Waking cortisol			
Waking pain	0.0629	3.347	0.008
Abuse history	0.3364	3.464	0.005
CES-D score	0.0048	1.196	0.274
Age	0.0052	0.964	0.356
Day	−0.0317	−0.341	0.737
1 hour cortisol			
1 hour pain	0.0624	2.974	0.011
Abuse history	0.3362	3.154	0.011
CES-D score	0.0020	0.392	0.704
Age	0.0075	1.318	0.219
Day	−0.0047	−0.049	0.962
5 hour cortisol			
5 hour pain	0.0247	1.889	0.078
Abuse history	0.0370	0.546	0.597
CES-D score	−0.0014	−0.420	0.684
Age	0.0000	0.009	0.993
Day	−0.0214	−0.583	0.577
9 hour cortisol			
9 hour pain	0.0069	0.668	0.517
Abuse history	0.0715	1.294	0.226
CES-D score	0.0041	1.391	0.194
Age	0.0017	0.552	0.593
Day	−0.0228	−0.796	0.465
Bedtime cortisol			
Bedtime pain	−0.0022	−0.327	0.749
Abuse history	−0.0275	−0.764	0.465
CES-D score	−0.0023	−1.298	0.231
Age	0.0018	0.928	0.382
Day	−0.0060	−0.206	0.839

* CES-D = Center for Epidemiologic Studies Depression Scale.

cortisol pattern may differ in women with FM according to whether there is a history of abuse (Figure 2B).

Momentary salivary cortisol level and patients' symptoms among women with FM. Mean unadjusted cortisol levels and ratings of pain symptoms at the 5 time points are shown in Figure 3. Among women with FM, ratings of momentary pain symptoms were strongly associated with cortisol levels at the waking and 1 hour time points, but not at the 5 hour time point, 9 hour time point, or bedtime (Table 2). These results did not change in models that included all data on all women with FM in the original patient study group. Cortisol level alone explained 38% and 14% of the pain variance at the waking and 1 hour time points, respectively.

To determine if the daily HPA axis "starting point" value might influence pain symptoms later in the day, regression models were performed to examine the relationship between salivary cortisol levels at the waking time point and pain symptom ratings at each of the later 3 time points; none of the associations were found to be significant. Moreover, there was no association between cortisol level and ratings of stress or fatigue symptoms at any of the 5 time points (for example, at the waking time point, $t = 1.21, P = 0.27$ for the relationship between cortisol and stress; $t = 1.27$, $P = 0.23$ for the relationship between cortisol and fatigue). There was no association between wake-up time and wake-up cortisol level ($t = 0.64$, $P = 0.56$).

Association between sleep quality measures and waking cortisol level and waking symptoms among women with FM. The association between sleep quality (average nocturnal activity level, sleep fragmentation index, and sleep efficiency level) and waking cortisol level and waking symptoms was also assessed by linear regression analysis. There was no association between the 3 sleep-related measures and waking cortisol level (for example, $t = 0.26$, $P = 0.63$ for the relationship between sleep efficiency and waking cortisol levels; $t = 0.01$, $P = 0.92$ for the relationship between sleep fragmentation index and waking cortisol levels). Furthermore, there was no association between these 3 measures of sleep quality and waking pain or stress levels (for example, $t = 0.02$, $P = 0.99$ for the relationship between the sleep fragmentation index and pain levels). Ratings of fatigue at the waking time point were associated with the sleep fragmentation index, showing a trend toward significance ($t = 1.84$, $P = 0.09$); there was no association between waking fatigue level and the other 2 sleep quality measures.

Characteristics associated with a stronger correlation between pain symptoms and cortisol level. For each woman with FM, the correlation between pain symptoms and cortisol level was calculated across days and time points, and the association between this value and patients' symptom characteristics was assessed (Table 3). A stronger correlation between pain symptoms and cortisol level was associated with a perception of worsening health on the SF-36, and with increased anger symptoms on the STPI. In addition, a stronger correlation between pain symptoms and cortisol level showed an association with increased STPI anxiety symptoms, with a trend toward significance. The strength of the association between pain symptoms and cortisol level was not due to the degree of elevation in cortisol ($t = -0.97$, $P = 0.34$ for the association between mean morning cortisol level and strength of association between pain symptoms and cortisol level, adjusted for age, depression symptoms, and abuse history).

Table 3. Partial correlation between selected symptom characteristics and amount of correlation between salivary cortisol levels and pain symptoms among women with fibromyalgia*

Characteristic	r	*P*
Symptom score		
Mean ambulatory pain	−0.082	0.762
Mean ambulatory fatigue	−0.197	0.464
Mean ambulatory stress	−0.397	0.128
STPI anger	−0.539	0.038
STPI anxiety	−0.508	0.064
CES-D, SD	0.004	0.990
SF-36 subscale		
Change in health (worsening health)	−0.604	0.017
Bodily pain	−0.293	0.289
General health	0.171	0.541
Physical functioning	−0.104	0.713
Social functioning	−0.157	0.576
Role—emotional	−0.140	0.620
Role—physical	−0.229	0.411
Vitality		
Sleep duration by actigraphy	−0.186	0.508

* STPI = State-Trait Personality Inventory; CES-D = Center for Epidemiologic Studies Depression Scale; SF-36 = Short Form 36.

DISCUSSION

Among participants in our sample, there was no difference in baseline cortisol secretion between FM patients and healthy control subjects. The similar pattern of age- and sex-adjusted cortisol secretion among FM patients and controls is consistent with the heterogeneous results of previous studies of cortisol secretion in FM, which have often failed to find group differences in various HPA axis measures between FM patients and healthy subjects (40). Among the women with FM in our sample, those who reported a history of physical or sexual abuse had a lower waking cortisol level and decreased diurnal cortisol variation compared with those not reporting a history of abuse. Participants of studies of HPA axis function in FM are often recruited from tertiary care clinic populations in which the prevalence of self-reported abuse among FM patients can be 50% or higher (20,41,42). Because of this high prevalence of abuse, assessing participants for a history of abuse and for other forms of early life stress may be important when examining HPA axis function in FM.

Among women with FM, the cortisol level was associated with current pain symptoms upon waking and at 1 hour after waking, but not at the later time points. At these 2 early time points, the cortisol level explained 38% and 14% of the variance in pain symptoms. Patients' pain symptoms tended to generally increase or remain stable during the later portion of the day, whereas cortisol values declined. The factors that limit the strong association between cortisol level and pain symptoms to the earlier part of the day are unknown, but may be related to relatively low levels of cortisol later in the day and/or a greater influence of other factors, such as daily activity level as the day progresses.

The association between cortisol levels and pain symptoms in FM does not imply causality. Cortisol level may influence pain symptoms, pain symptoms may influence cortisol level, and/or cortisol and pain symptoms may be associated via a third variable. The mechanisms by which cortisol might influence pain in FM remain speculative. As noted above, in studies examining the immediate effects of cortisol levels in healthy controls, elevated cortisol levels have been associated with increased negative mood, anxiety, and fear (15–19). Such psychological factors have been found to influence brain activity in pain-sensitive brain regions (43), and thus cortisol may influence pain via short-term mood-induced alterations in CNS pain processing. Individuals with increased anger and anxiety symptoms may be more vulnerable to this influence, which would account for this finding in our sample.

Candidate neurotransmitters through which cortisol might influence pain symptoms include serotonin (5-HT) and norepinephrine (NE). The HPA axis and central 5-HT appear to be closely interrelated; glucocorticoids influence 5-HT_{1A} receptor density and 5-HT synthesis (44,45), and in patients with depression who are treated with serotonergic antidepressants, corticotrophin-releasing factor concentrations are reduced (46). The HPA axis and central NE sympathetic systems also have interconnected function (47,48), and central NE systems appear to be involved in descending inhibitory pain control (49–52). Whether cortisol is capable of influencing pain via any of these mechanisms on a momentary basis is unknown.

In addition to its effects on the brain, cortisol may also influence pain processing via its actions at the spinal cord level or in the periphery. The important nociceptive functions of glucocorticoid receptors in the spinal cord dorsal horn have been increasingly recognized. Dorsal horn glucocorticoid receptors respond to peripheral nociceptive stimulation (53,54), modulate morphine-induced antinociception (55–57), and contribute to neuronal plastic changes resulting from neuronal injury (58). In the periphery, cortisol variation may influence the balance of peripheral proinflammatory cytokines, which might contribute to pain symptoms via peripheral or central mechanisms (59).

This study has a number of limitations that should be considered when interpreting the results. First, 24% of participant-days of data were eliminated due to nonadherence to protocol. This rate of nonadherence is similar to that among participants who were unaware of compliance assessment in a recent study by Broderick et al (60). As in that study, our findings suggest that patients with FM are more compliant with research protocols than are healthy controls. The exclusion of nonadherent participants is likely to increase internal validity; however, these exclusions resulted in a relatively small control group and a markedly different sex distribution between groups. This limits the generalizability of our comparisons between FM patients and control participants. It is somewhat reassuring that the adjusted mean morning cortisol level of control participants in our sample (0.37 μg/dl, or 10.2 nmoles/liter) is very close to the mean morning cortisol level of the 22 control participants (73% women) in another naturalistic salivary cortisol study (slightly higher than 10 nmoles/liter, as shown in Figure 1 of Catley et al [6]).

A related issue is that the relatively small sample size, after exclusions, limited our statistical power to detect group differences in diurnal cortisol secretion. This limited statistical power increases the risk that meaningful differences in salivary cortisol levels between groups may have been missed. Of note, power estimates based on *t*-tests using observed mean cortisol values and standard deviations at each time point indicate that to identify even the largest effect size observed between FM patients and control participants with a power of 0.8 (at the fifth time point) would have required 89 participants per group. At other time points, several hundred participants per group would have been required to identify group differences. In contrast, because of the much larger effect sizes observed between women with FM reporting a history of abuse and those not reporting a history of abuse, 30 women with FM in each group would be sufficient to identify between-group differences at the first, second, and fifth time point. Future studies should consider these issues and plan for comparable rates of nonadherence when estimating sample size requirements.

Similarly, the small sample size could also have prevented us from identifying significant associations between fatigue and stress symptoms and momentary cortisol levels. Such associations, if present, are likely to be far weaker than the association between pain symptoms and momentary cortisol level, given that a robust association between pain symptoms and cortisol level was present at some time points, and that tests of association between fatigue and stress symptoms and the momentary cortisol measurement were not significant, even if the alpha level was increased from 0.05 to 0.20.

The wake-up time of FM patients was earlier than that of the controls, which would tend to increase the morning cortisol level (61) in the patients with FM compared with the controls. However, although this influence would have increased the difference in waking cortisol levels between the groups, no significant difference in waking cortisol levels between groups was found. Also, fixed-time measurements were chosen for the study, in order to provide a better ability to compare diurnal cortisol levels between groups. This design increases the possible influence of participant expectation; future studies should consider using a random sampling strategy to minimize this possible influence. Furthermore, because of its naturalistic design, this study did not control for the breadth of daily experiences that might influence baseline cortisol levels.

Another study limitation relates to the manner in which abuse history was assessed. Study participants were asked if they had ever been physically or sexually abused, but were not asked behaviorally specific questions (e.g., "Did anyone ever touch your genitals when you didn't want them to?"). Abuse in this study was thus not specifically defined, and the definition relied solely on participants' own label of their past experience. This kind of label-only abuse assessment is a relatively insensitive method of identifying abuse victims compared with asking behaviorally specific questions, because a significant number of victims do not label their experiences as abuse (62,63). Thus, our method of identifying abuse history may not have identified all participants with an abuse history in the study. Error in classification would tend to lead to an underestimation of the true differences between those with and those without self-reported abuse, and could increase the inaccuracy of regression model estimates. However, the prevalence of self-reported abuse among FM patients in our sample is similar to that reported in other FM tertiary care populations (20,41,42), and the validity of the brief self-report measure used in the study is supported by the nature of the HPA axis changes found among those reporting abuse, which are consistent with the known biologic affects of early life stress (20,21).

Simple 10-point Likert scales were used to assess patients' pain, fatigue, and stress symptoms. It is possible that more sophisticated measures of stress or fatigue would have yielded different findings from these simple assessment measures. Simple, brief symptom measures were used in an attempt to maintain the naturalistic

quality of the study by minimizing disruption from participants' daily activities at each assessment. Similarly, sleep quality was assessed via relatively simple actigraphy-based measures. Such measures may be an optimal method of assessing sleep quality in naturalistic studies, but they have not been validated and their relationship to gold standard sleep laboratory assessments is not known. Finally, because no general self-report measure of recent perceived stress was used, the influence of recent perceived stress on cortisol levels, pain, and the correlation between cortisol and pain could not be assessed.

The results of this study indicate that pain symptoms in women with FM are associated with cortisol concentrations during the early part of the day, but not at later time points. These data support the hypothesis that HPA axis function is associated with symptoms in FM and accounts for the substantial percentage of pain symptom variance during the early part of the day. However, this study does not determine if these changes in cortisol level play any role in causing pain or are, instead, caused by the pain. Further studies examining the relationship between cortisol level and pain symptoms in FM and in other chronic pain disorders are needed to confirm this finding and to determine the mechanisms involved in the association between momentary cortisol level and pain.

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Fibromyalgia Syndrome

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ABSTRACT. The objectives of the first OMERACT Fibromyalgia Syndrome (FM) Workshop were to identify and prioritize symptom domains that should be consistently evaluated in FM clinical trials, and to identify aspects of domains and outcome measures that should be part of a concerted research agenda of FM researchers. Such an effort will help standardize and improve the quality of outcomes research in FM. A principal assumption in this workshop has been that there exists a clinical syndrome, generally known as FM, characterized by chronic widespread pain typically associated with fatigue, sleep disturbance, mood disturbance, and other symptoms and signs, and considered to be related to central neuromodulatory dysregulation. FM can be diagnosed using 1990 American College of Rheumatology criteria. In preparation for the workshop a Delphi exercise involving 23 FM researchers was conducted to establish a preliminary prioritization of domains of inquiry. At the OMERACT meeting, the workshop included presentation of the Delphi results; a review of placebo-controlled trials of FM treatment, with a focus on the outcome measures used and their performance; a panel discussion of the key issues in FM trials, from both an investigator and regulatory agency perspective; and a voting process by the workshop attendees. The results of the workshop were presented in the plenary session on the final day of the meeting. A prioritized list of domains of FM to be investigated was thus developed, key issues and controversies in the field were debated, and consensus on a research agenda on outcome measure development was reached. (J Rheumatol 2005;32:2270–7)

Key Indexing Terms:
FIBROMYALGIA CHRONIC PAIN OMERACT OUTCOME MEASURES

Introduction and Background

Fibromyalgia (FM), as defined in the 1990 American College of Rheumatology (ACR) criteria[1], is a chronic, generalized pain condition with characteristic tender points on physical examination, often accompanied by a number of associated symptoms such as fatigue, sleep disturbance, headache, irritable bowel syndrome, and mood disorders. By this definition, FM affects at least 2% of the adult population in the US[2]. Although our understanding of the etiology of FM is evolving, evidence shows that the syndrome is influenced by factors such as stress, medical illness, and pain conditions in some, but not all patients, as well as a

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variety of neurotransmitter and neuroendocrine changes[3,4,4a]. Such changes include reduced levels of biogenic amines, increased concentrations of excitatory neurotransmitters, and alterations of hypothalamic-pituitary-adrenal axis and autonomic nervous system activity[5]. A range of treatments are employed to treat the various symptom facets of FM[3,4a,6]. These include neuromodulatory medications such as antidepressants, opioids, nonsteroidal antiinflammatory drugs, sedatives, muscle relaxants, and anti-epileptics. Nonpharmaceutical treatment modalities, including education, exercise, physical therapy, massage, and cognitive behavioral therapy, can be helpful for FM as well[4a,7-10]. Although some of these therapies have been tested in randomized controlled trials (RCT), there has been little standardardization of an approach to trials or of outcome measures used. This represents a challenge for regulatory agencies that have yet to approve a drug for FM. They must ask a series of fundamental questions: What constitutes meaningful symptomatic change for an FM patient? How can change be accurately and consistently measured in this population? How durable is the therapeutic effect?

Evaluating therapeutic effects in FM is difficult because of the many facets of the syndrome. Diagnostic criteria based on pain and tender points have been developed for research purposes and identify a group of patients with pain and tenderness[1]. However, subgroups of patients with differing intensity of symptoms have been reported, and the current criteria may be shown to be limiting as further understanding about pathophysiology emerges[4,11]. Outcome measures transplanted from pain, rheumatology, neurology, and psychiatry research are able to distinguish treatment response in individual symptom domains, but do not necessarily tell us if meaningful change has occurred, either in individual symptom domains or the syndrome as a whole. Further work is necessary to refine and validate these measures in FM, as well as develop composite measures or response criteria to address the multidimensional nature of the syndrome. As more potential treatments for FM are being tested, there is pressing need to develop and standardize valid and reliable instruments to measure outcomes, which will improve the comparative value of treatment trials.

A possible model for this endeavor in FM, in the field of pain medicine, is that of the IMMPACT group (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials)[12,13]. As a partnership between researchers, industry, and the US Food and Drug Administration (FDA), this group is addressing the question, "What should be the core outcomes to assess in chronic pain clinical trials?" The consensus of this group has been that key outcomes to consider should be pain, physical functioning, emotional functioning, patient global ratings of satisfaction, negative health states, adverse events, and patient adherence and disposition.

Review of Instruments of Assessment of FM

Disease-specific composite measures. A disease-specific composite measure has been developed and validated in FM. The Fibromyalgia Impact Questionnaire (FIQ), developed by Burckhardt and coworkers, consists of questions and visual analog scales regarding functional disability, pain intensity, sleep function, stiffness, anxiety, depression, and overall sense of well-being[14]. Criticisms of the FIQ are that it may underestimate disease impact and inadequately measure treatment effect in patients with mild symptoms, and it is not validated in men. In addition, the functional assessment has been criticized as containing items not routinely performed[15]. Nevertheless, the FIQ is responsive to change and has been translated into many languages[16]. Assessing function, a component of the FIQ, has proved difficult in this population. A number of instruments have been used, but have not been consistently responsive to change[15]. Although the FIQ has been used as a measure of overall health status in patients with FM, the functional component is oriented toward high levels of disability, resulting in a potential floor effect[15]. In a controlled trial of fluoxetine in FM, the physical impairment subscore of the FIQ did not significantly improve in the fluoxetine-treated patients compared with placebo, although the total score did significantly improve in the fluoxetine group. No other FM-specific instruments that measure function have been tested in clinical trials. The Medical Outcome Study (MOS) Short Form-36 (SF-36) has been used to assess some aspects of function and quality of life in trials of FM, with inconsistent results[17–25].

Pain assessment. A standard tool of pain assessment is the daily pain diary, which is intended to assess pain intensity as well as the impact of pain on function[18]. The daily results are typically averaged on a weekly basis, and change from baseline to study endpoint is the primary outcome measure. Problems with this methodology include recall error, compliance with daily recording, and change in the patient's evaluation of pain intensity and impact over the length of the study. Efforts to deal with these problems have included use of the electronic diary and evolving methodologies of pain scaling methods[18]. The McGill Pain Questionnaire (MPQ) is a commonly employed pain questionnaire[26]. It includes 78 pain-related adjectives subdivided into sensory, affective, evaluative, and miscellaneous sensory qualities of pain. A shorter SF-MPQ, which includes 15 adjectives in sensory and affective categories, has been utilized in FM[26]. The SF-MPQ has been used in several trials and is able to distinguish drug versus placebo[19-22,24,25]. The Brief Pain Inventory (BPI) is a questionnaire that assesses intensity, impact, quality, relief, and patient perception of cause of pain[27]. It has been shown to be discriminant in recent FM trials[20,21]. The Leeds Assessment of Neuropathic Symptoms and Signs is an outcome measure designed to distinguish neuropathic and nociceptive pain. It was able to distinguish

quality of pain between patients with rheumatoid arthritis versus FM[28].

The manual tender point examination has been historically considered a key feature in the definition of FM[1]. However, validity and utility of the manual tender point examination is increasingly questioned: (1) Many patients who fall within the FM paradigm may have fewer than 11 tender points. (2) The manual tender point examination is limited by the relative lack of objectivity of the findings. (3) There is an uncertain relationship between the tender point examination and the underlying pathophysiology of the syndrome[4].

Although the manual tender point examination distinguishes FM patients from controls, its discriminant ability in clinical trials has been variable, suggesting that it may be useful as an entry criterion but not as an outcome measure. Dolorimetry, which may improve objectivity in tender point examination[29], has been shown to be responsive to treatment in a recent clinical trial[20]. Manual tender point intensity has been assessed utilizing the Fibromyalgia Intensity Score[30], in which the patient describes pain intensity on a 0–10 scale and the scores of 18 sites are averaged.

Fatigue assessment. The Multidimensional Assessment of Fatigue index, an 18 item questionnaire, has been used in FM trials[22,31,32]. The Multidimensional Fatigue Index, which similarly measures multiple aspects of fatigue including the emotional and physical, has been validated in a variety of populations and diseases, although not yet in FM[33]. Other instruments include the Functional Assessment of Chronic Illness Therapy[34] and the Fatigue Severity Scale[35]. The advantage of such tools is their ability to explore the multiple dimensions of fatigue. Simpler, single-question fatigue assessments are embedded within such composite instruments as the FIQ.

Sleep assessment. Multiple dimensions of sleep quality have been variably assessed in FM trials, including quantity, quality, ease of falling asleep, frequency of waking, and feeling refreshed upon awakening. Instruments include the MOS sleep scale[36], as well as single-question assessments of sleep quality in a daily diary format and embedded in the FIQ.

Quality of life and global assessment. Several instruments have been used to measure quality of life and global assessment in FM. The Patient Global Impression of Change[24], measured on an 11 point scale, and the Patient Global Impression of Improvement[20,21], measured on a 7 point scale, have been shown to discriminate treatment effect in FM. The MOS SF-36 used in most FM trials has 8 subscales assessing physical and mental function[37]. Several physical and mental subscales have been shown to discriminate treatment effect in FM[20-22,24].

Sexual function assessment. Sexual function is an important dimension of quality of life that is often overlooked in clinical trial outcome assessment. This domain can be improved as a person feels better with treatment, or sometimes worsened, e.g., as a side effect of some antidepressant or pain medications. A measure of sexual function has been utilized in one recent FM trial[24,38].

Assessment of psychiatric symptoms and comorbid psychiatric disorders. A number of screening tools for assessment of depressive and anxiety symptoms have been used in FM clinical trials, including the Beck Depression Inventory and the Beck Anxiety Inventory[39,40], the Hospital Anxiety and Depression Scale[41], and the Hamilton Depression Rating Scale[42]. The Mini International Neuropsychiatric Interview[43] and the Structured Clinical Interview for the DSM-IV Axis I Disorders[44] are structured diagnostic interviews that have been used for the diagnosis of comorbid psychiatric disorders in some FM trials. These structured interviews serve to exclude patients with certain psychiatric diagnoses for safety reasons, or stratify patients to observe if there are differences in treatment outcomes relative to these comorbid diagnoses. A comprehensive review of psychiatric measures in FM has been recently published[45].

Responder analyses. What constitutes a "meaningful" response in FM? Regarding pain response, Farrar has published a pooled analysis of patients with chronic pain of various etiologies, including FM, treated with pregabalin. In this analysis, a 30% reduction in the pain intensity score was considered a clinically important difference, and a 50% reduction was associated with the highest degree of improvement[46]. Regarding response of the syndrome as a whole, 2 groups have proposed different composite criteria sets, which are a weighting of measures such as pain, tender point assessment, function, and sleep quality[47,48]. These proposed sets have not been used in recent clinical trials nor recommended by regulatory agencies. However, they are examples of a potentially valuable composite criteria set for evaluating FM as a whole, and not just individual domains of the syndrome.

Delphi Exercise on FM Domains

Objective and background. A Delphi exercise among FM researchers was conducted prior to the OMERACT workshop to develop consensus on a prioritized list of key domains of the FM syndrome that should be addressed in clinical trials (Table 1 and Table 2). The steering committee of the workshop considered it important to have a framework of prioritized domains to present at the OMERACT workshop as a basis for discussion and for developing a research agenda on domains of inquiry and instruments of assessment in FM trials.

The exercise was modeled after a recently completed Delphi exercise conducted by GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis). The key elements of a Delphi process were in place: (1) Anonymity — questionnaires were E-mailed; (2)

Iteration — 3 "rounds" were conducted; (3) Controlled feedback — individuals were informed of the whole-group response after each round; and (4) Statistical group response — group judgment was expressed as the median; spread of opinion indicated strength of consensus[49-53].

Methods. A list of 40 potential domains was prepared through literature review and E-mail discussion by steering committee members (see Table 1). After the domains were established, a selected group of FM clinicians and researchers was asked to participate in the consensus exercise. Fifty-one potential participants were contacted; 23 completed all 3 rounds of scoring. Each participant was e-mailed the list of 40 domains in Microsoft Excel spreadsheet format and asked to distribute 100 points among the domains, giving more points to domains they considered more important to evaluate. In 2 subsequent rounds the results of the group median, interquartile range, and total range of the earlier responses were E-mailed to each respondent, who could reflect on previous scoring and revise subsequent scoring if they chose. The participants were asked to rank the domains in each of 3 different contexts: (1) Symptom Modifying, i.e., as might be considered important in a clinical trial; (2) Clinical Record Keeping, i.e., as might be considered important in recording in a medical chart; and (3) Rehabilitation, i.e., as might be considered important regarding ultimate ability to improve or achieve remission. For the workshop, only data from the Symptom Modifying context were reviewed and discussed.

Results. The results are presented in Table 2. Pain was considered the key domain to be assessed, followed by fatigue, patient global, and sleep. Other key domains are indicated.

Table 1. Delphi symptom domains as a complete list.

Abuse, alcohol and/or drug use	Negative cognitive factors
Abuse, physical, sexual, and/or emotional	Noxious threshold
Anxiety diagnosis, current or previous	Pain
Arthralgias	Paresthesia/dysesthesia
Chest pain	Personality disorder
Comorbities, influence of	Physical functioning
Depression, current or previous	Productivity
Dyscognition	Restless leg syndrome
Family/social construct	Satisfaction
Fatigue	Secondary gain
Global clinician-rated improvement	Sexual function
Global patient-rated improvement	Sicca symptoms
Headache	Sleep quality
Health-related quality of life	Social functioning
Income	Socioeconomic status
Irritable bladder syndrome	Symptoms, number and level of
Irritable bowel syndrome	Tenderpoint count
Marital status	Tenderpoint intensity
Morning stiffness	Treatment side effects
Muscle fatigue or weakness	Unresponsivness to treatment

Table 2. Median Delphi scores for 12 domains identified for clinical trials of FM

Domain	Median Delphi Score
Pain	16
Fatigue	10
Patient global	10
Sleep quality	8
Health related quality of life	5
Physical function	5
Treatment side effects	5
Depression	5
Tender point intensity	2
Dyscognition	2
Anxiety diagnosis	2
Clinician rated global	1

FM Workshop Session at OMERACT 7

The Delphi exercise was presented, followed by a review of major clinical trials in FM, with a focus on the outcome measures used, in order to build an understanding of the key symptomatic domains that underlie the syndrome and their responsiveness to therapy. Trials chosen for review included those of tricyclic antidepressants (TCA)[19], fluoxetine[54], tramadol plus acetaminophen[23], tramadol[55], pregabalin[22], duloxetine[20], recombinant growth hormone[25], and milnacipran[24]. Some of these studies are unpublished except in abstract form, therefore the data have been anonymized in this report. The results were translated into standardized effect sizes by dividing the placebo-corrected difference by the pooled standard deviation using the method of Cohen[56]. Effect sizes of 0.2–0.49 are generally considered small, 0.5–0.79 are considered medium or moderate, and > 0.8 are considered large. These results are summarized in Table 3. Domains assessed, utilizing measures outlined previously, included pain (by VAS, multidimensional), fatigue (VAS, multidimensional), sleep (VAS, multidimensional), patient and clinician global assessment of change, function (by the FIQ), health-related quality of life (SF-36), depression, and anxiety. Effect sizes for all domains tended to be medium in size, and patients with FM show weaker correlations between improvement in symptoms and improvement in physical function than in other rheumatic diseases. These studies provide understanding of the responsiveness of FM to treatment and the endpoints most sensitive to improvements in symptoms and function.

Tramadol and tramadol/acetaminophen for the treatment of FM. Two trials, tramadol alone and tramadol in combination with acetaminophen, demonstrated modest efficacy in treating FM pain[23,55]. Tramadol/acetaminophen had modest effects on function as assessed by FIQ and SF-36. Tramadol alone did not improve function as assessed by FIQ total score. Tramadol/acetaminophen had no effect on sleep. Sleep was not assessed in the trial of tramadol alone.

Table 3. Effect sizes observed in clinical trials of therapeutic agents in fibromyalgia.

Drug	Duration	Pain				Sleep	Fatigue		Mood		Global		Function
Outcome	No. of Studies	VAS Pain	SF-36 Bodily Pain	Tender Points	Morning Stiffness	Sleep	Fatigue	SF-36 Vitality	Mood Anxiety	Mood Depression	Patient Global	FIQ Total	SF-36 Physical Function
A	1–8 wks	0.78	0.55	0.29		0.82	0.46	0.42	0.20	0.19			0.22
B	Average across 9 studies	0.52		0.29		0.66	0.45				0.66		
C	1–12 wks	0.95		0.48	0.52		0.57						
D	1–12 wks	0.34		0.41	0.24		0.08				0.24		
E	1–12 wks	0.39	0.39	0.22	0.32	0	0.13	0.15	0.27	0.13		0.37	0.33
F	1–9 wks	0.49		0.18								0.11	
G	1–12 wks	0.51	0.4			0.25	0.41	–0.02	0.26	0.25			
H	1–9 mo			0.6								0.6	

Recombinant human growth hormone. Use of growth hormone (GH) in FM is based on studies showing that levels of insulin-like growth factor-1 (IGF-l, the mediator of GH activity) in patients with FM are lower than in age-matched controls. Whether lower IGF-1 is a result of the FM syndrome or involved in the causative pathway is not known; however, IGF-1 does play a role in muscle repair, and thus could conceivably be involved in the pathogenesis of FM pain[57]. A 9-month study of injectable recombinant human GH in patients with a low IGF-1 at entry showed improvements in FM symptoms as assessed by the FIQ total and tender points score[25].

Tricylic antidepressants. In a metaanalysis of TCA[19], most studies used a pain VAS or Likert scale as the primary outcome. Sleep, fatigue, tenderness, stiffness, and mood/anxiety were frequently assessed as secondary outcomes. Global assessment and a variety of health related quality of life (HRQOL) and functional assessments were measured. TCA generally had moderate effects on sleep and pain, with the effects on sleep generally slightly larger.

Selective serotonin reuptake inhibitors (SSRI). Although the effect of SSRI on pain has been marginal, one study of flexibly dosed fluoxetine showed improvement of pain, as measured by FIQ pain score, and statistically significant effects on fatigue and depression[54].

Serotonin/norepinephrine reuptake inhibitors (SNRI). Milnacipran was efficacious in treating the core symptoms of FM, including pain, fatigue, and mood[24]. Robust improvements were observed in the Patient Global Impression of Change, with modest effects on fatigue and functioning (measured by FIQ) and small effects on sleep. Patients demonstrated improvements in pain regardless of baseline major depressive episode status, but patients with depression had the largest placebo response on pain scales. Duloxetine, another SNRI, was tested in FM patients. In the first of 2 studies, significant improvement was demonstrated in the treated group utilizing the total FIQ score, but did not show significance in the co-primary outcome of FIQ pain score, nor was improvement noted in male subjects[20]. A secondary outcome measure of pain, the BPI, did show statistically significant improvement in the treated group. Duloxetine also improved several other symptoms associated with FM, including stiffness and tender points (measured by dolorimetry), as well as global assessment and several quality of life measures. Duloxetine improved pain symptoms regardless of baseline major depressive disorder status. A second study, utilizing the BPI as a primary pain endpoint and excluding male patients, did show statistically significant improvement[21].

Pregabalin. Pregabalin is an investigational agent that binds to the alpha-2-delta subunit of the voltage-gated calcium channel in the central nervous system. It is structurally related to gabapentin and is being developed for the treatment of FM and other indications. Pregabalin was studied in an 8 week RCT in FM and was efficacious in the treatment of pain, sleep disturbance, and fatigue[22]. The primary outcome was pain measured by an 11-point numeric rating score recorded in a daily pain diary. There was significant improvement in pain at the highest dose studied. Significant improvement in sleep was also observed as assessed by a sleep diary and the Medical Outcomes sleep scale. Significant reduction in fatigue was also reported. Patient global impression of change and 4 domains of the SF-36 were also improved.

Cognitive behavioral therapy. A trial of cognitive behavioral therapy (CBT) in chronic multisymptom illness (CMI) showed correlation estimates between the SF-36 physical component scale and pain (0.34), general fatigue (0.40), and physical fatigue (0.42)[58]. This cohort with CMI had extremely low levels of self-reported function, like other cohorts with FM. CBT specifically aimed at improving physical function had only a marginally significant influence on self-reported physical function. This and other studies suggest weaker correlations between improvements in

symptoms (e.g., pain, fatigue, etc.) and improvement in function in FM than in other rheumatic disorders. A second clinical trial of CBT in FM using similar methods and outcome measures showed patients receiving CBT to be twice as likely to have a clinically meaningful improvement in physical functional status than standard care[59].

US regulatory perspective on FM. Jim Witter of the FDA Arthritis Advisory Committee highlighted the presentation and discussion of the committee's meeting on FM of June 23, 2003[60], and the US National Institutes of Health-FDA Guidance on Analgesics (under revision and currently not available). Unmet needs in chronic pain include a need for better understanding of clinical aspects of chronic pain and the pain mechanisms that may serve as treatment targets, and for standardized and validated methodologies of trial design and outcome measurement in FM. The FDA is currently considering 2 non-mutually exclusive approaches for new therapeutic agents seeking a claim approval for FM: (1) for symptomatic management of pain of FM, and (2) for the management of FM as an overall syndrome. To achieve the former, the drug would need to show statistical superiority in a predetermined pain measure(s). To achieve the latter, the drug would need to also show statistical superiority in its effect on a broader arena of symptoms and function of FM patients. Regarding recommendations as to a core set of domains to be considered in clinical trials of FM, the model of the IMMPACT recommendations was described[12,13]. Ultimately, a composite responder analysis, akin to the ACR-20 response criteria for rheumatoid arthritis, would be highly desirable for future trials of pharmacologic agents in FM.

OMERACT Workshop Consensus Voting

After reviewing the pre-OMERACT Delphi exercise and the data from clinical trials in FM patients, workshop attendees prioritized domains of assessment for clinical trials. Results are presented in Tables 4 and 5.

The key difference from the pre-OMERACT Delphi prioritization is a higher ranking of HRQOL and function, with a focus on multidimensional aspects of function rather than simply physical function. There was acknowledgment that aspects of function such as role, vocational, and emotional function may be of as great or greater importance in a patient with FM than physical function limitations. As in the prior Delphi exercise, pain, fatigue, and patient global sense of well-being ranked highest. The group also agreed that those domains ranked by at least 50% of workshop attendees should be considered key domains to assess in clinical trials, whereas those ranked lower should be considered to be measured, but that more research would be necessary to know how critical they would be, and how best to measure them. There was support for placing the concept of "participation" on the research agenda, i.e., developing an approach to measure ability of patients to participate in life activities and function. There was also support for further development of a new composite instrument and/or an outcome criteria set for FM, analogous to the ACR or DAS criteria sets used in rheumatoid arthritis. The group was split on whether this should be in the form of a responder analysis or on a continuous scale. It was recommended that the patient perspective be included in the prioritization of research domains, which could be accomplished by a future Delphi exercise with patients.

Table 4. Percentage of OMERACT workshop attendees who considered domains essential to assessment in clinical trials of fibromyalgia.

Domain	Respondents (%)
Pain	100
Patient global	94
Fatigue	85
Health related quality of life	76
Multidimensional function	75
Sleep quality	70
Depression	65
Treatment side effects	58
Physical function	42
Clinician rated global	23
Dyscongnition	21
Anxiety diagnosis	21
Tender point intensity	18

Table 5. Voting results from FM workshop exercise. Attendees were asked to rank which domains that they thought were most important, and second and third most important to measure in FM studies.

Domain	Percentage of Attendees Who: Ranked First	Ranked Second	Ranked Third	Ranked in Top 3
Pain	64	13	16	93
Patient global	22	18	25	65
HRQOL	12	16	20	48
Fatigue	0	32	24	56
Sleep	2	13	4	19
Physical function	0	7	9	16

Conclusions

The primary objective of the FM workshop, to establish a prioritized list of domains key to FM research, was achieved with the ranking of the following key domains: pain, patient global, fatigue, HRQOL, function (multidimensional), sleep, depression, and treatment side effects. Other important domains, not considered as essential, included physical function, tender point intensity, dyscognition, anxiety, and clinician global assessment. This ranking is consistent with that achieved prior to the workshop in a Delphi exercise of FM researchers (Table 2). Highlighted is the multidimensional nature of the FM syndrome, with its key elements of pain, fatigue, sleep disturbance, and functional disability.

There exist a variety of outcome measures, outlined in this article, to assess these domains and that have been used in FM clinical trials. Following further standardization and validation they will constitute the core of the upcoming research agenda for the FM research community. Further key research objectives will be to refine measures of the multidimensional aspect of functional disability, including role vocational, social, and emotional aspects, addressing the concept of "participation" as an outcome measure, to include patient perspective on what represents a clinically meaningful change in a domain or the syndrome as a whole. Toward this end, focus groups of FM patients are being developed to address the patient perspective and to serve as a nucleus for conduct of Delphi exercises. There is consensus that development and validation of a composite instrument and/or criteria set for fibromyalgia as a syndrome is of key importance. Several members of the Steering Committee are currently involved with an ongoing project to develop and validate such a measure. Results of these research efforts will hopefully be discussed in the next OMERACT session in 2006.

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Differences in unpleasantness induced by experimental pressure pain between patients with fibromyalgia and healthy controls

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Abstract

Pain possesses both sensory and affective dimensions, which are highly correlated yet distinct. Comparison of these dimensions within experimental pain settings has resulted in the construct of relative unpleasantness. Relative unpleasantness is defined as the amount of affective unpleasantness elicited for a given sensory magnitude. The aim of this study was to determine the relationship between affective and sensory components of evoked pain in subjects with fibromyalgia (FM) and healthy controls. Here we show that patients with FM unexpectedly display less relative unpleasantness than healthy controls in response to random noxious pressure stimuli. Relative unpleasantness was not correlated with distress, anxiety, or depression, which were pronounced in the FM group. Clinical pain in patients with FM was perceived to be more unpleasant than the evoked pain stimuli. These results are consistent with the concept that chronic pain may reduce the relative unpleasantness of evoked pain sensations.

Keywords: Fibromyalgia; Pain; Unpleasantness; Sensory; Affective

1. Introduction

Pain is a sensation that is composed of distinct yet inter-related dimensions. Pain can be described in terms of its intensity or sensory qualities as well as its emotional or affective aspects, which are integral to the sensation. Primary affective pain is believed to occur over a short period of time and is related to the minute-by-minute appraisal of pain, whereas secondary affective pain involves both past and future long-term reflection of the sensation or condition. A final cognitive-evaluative dimension integrates both past experiences and judgments and exerts control over activity of both the sensory and affective systems (Melzack and Casey, 1968). This model has evolved from studies of both experimental and clinical pain (reviewed in: Fields, 1999; Gracely, 1999; Price, 2000).

Different clinical pain states can have distinct sensory and affective qualities. Price et al. (1987) observed that although women in labor and cancer patients experienced pain of similar sensory intensity, the affective component or unpleasantness of their pain was markedly different. Cancer patients reported more unpleasantness associated with their pain than did women in labor. Furthermore the unpleasantness that women in labor experienced was altered by their cognitive state. Accordingly, attention

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and other cognitive processes appear to modify pain perceptions (Malow, 1981; Miron et al., 1989; Keogh and Mansoor, 2001; Geisser et al., 2003).

Investigations of experimentally induced pain have also shown a divergence between pain dimensions (Gracely et al., 1979; Rainville et al., 1992) and this separation may be manifested in different cortical brain regions and modulated by different neurotransmitters. For example, the neural activity in the somatosensory cortex (S1) appears to correlate with pain intensity (Hofbauer et al., 2001) while activity in the anterior cingulate cortex (ACC) and other limbic structures may be the locus for unpleasantness (Rainville et al., 1997). Similarly, the affective and sensory components of pain are differentially modulated by pharmacologic therapies (Gracely et al., 1979). Given this divergence of sensory and affective aspects for both clinical and experimental pain, it is useful to define the measure of relative unpleasantness as a construct to assess this difference (Rainville et al., 1992). Relative unpleasantness can be thought of as "how much a given sensation bothers you" (Gracely, 1992).

Strong affective elements make the syndrome of fibromyalgia (FM) ideal for examining differences in pain intensity and unpleasantness in both experimental and clinical settings. FM is defined by the presence of chronic, widespread pain, and the finding of generalized tenderness or increased pressure pain sensitivity on examination, as assessed by a tender point exam (Wolfe et al., 1990). A positive exam is defined by the presence of evoked pain at 11 out of 18 tender points when 4 kg of pressure is applied. In addition, FM patients commonly have high levels of psychological affective symptoms, such as anxiety and depression (Boissevain and McCain, 1991; Epstein et al., 1997), which could be an independent feature of the syndrome and/or a result from secondary aspects of this chronic condition. A complicating factor in FM studies is that the number of positive tender points has been shown to be influenced by an individual's subjective level of distress, so studies designed to isolate the affective component of the pain experience must control for this association (Wolfe, 1997; Petzke et al., 2003b).

More sophisticated experimental pain assessment methodologies may provide insight into the affective component of the pain experience in fibromyalgia. Most experimental pain studies in FM to date have used an "ascending" testing paradigm, such as manual tender point counts or dolorimetry, wherein the stimulus intensity is increased in a predictable manner (Bendtsen et al., 1997). Not surprisingly, subject and observer factors such as expectancy, affective state, or hypervigilance can influence pain report in these ascending paradigms (McDermid et al., 1996; Wolfe, 1997). Random testing paradigms, in which the next stimulus cannot be anticipated, have been shown to reduce these confounding factors (Petzke et al., 2003a,b), and are thought to minimize the biasing effect of distress in determining a patient's degree of tenderness.

This study quantitatively describes the sensory intensity and affective unpleasantness components of evoked pressure pain in FM subjects and healthy controls (HC). Ratings were obtained from both ascending and random methods of stimulus presentation to evaluate the role of bias as outlined above. The specific focus was to determine if FM subjects had altered pain unpleasantness in response to evoked pressure stimuli relative to HC and if this difference would be correlated with measures of distress, dysfunction and clinical pain.

2. Materials and methods

2.1. Subjects

Patients under treatment at the Georgetown University Medical Center for an established diagnosis of FM were invited to participate in the study. Concurrent inflammatory rheumatic conditions or severe other medical conditions were criteria for exclusion. HC subjects were recruited through flyers and newspaper advertisements, compensated for their participation, and matched by age and sex to the patient population. Prior to the study, all participants read and signed an informed consent form. The Georgetown University Institutional Review Board approved the consent form and study protocols.

Because previous studies have shown differences in pain report for women at different stages in the menstrual cycle (Bajaj et al., 2001, 2002; Riley et al., 1999), all female participants were screened for menstrual status on the day of pain testing. They were asked about menstrual history, average cycle length, last menstrual period, and use of medications (birth control pill, hormone replacement therapy). Cycle stages were grouped into menstruation, follicular (including midcycle), luteal (including premenstrual), and postmenopausal (including perimenopausal women, and subjects with hysterectomy).

For patients with FM the presence of chronic widespread pain was confirmed, and a manual tender point count performed. Only patients that satisfied the ACR criteria (Wolfe et al., 1990) of at least 11 of 18 positive tender points were included in the analysis. All control subjects underwent a tender point examination and were excluded if they had a tender point count of 11 or greater or a history of any current or chronic pain of greater than one-week duration.

2.2. Psychophysical testing – overview

Upon arrival to the research center all subjects were shown and oriented to the experimental pain-testing environment. During that time the consent form was signed

and remaining questions answered, the menstruation history obtained, and subjects were asked about current medications and their intake in the last 24 h. Patients participating in pain testing were allowed to continue their regular medication. However, they were advised not to take any analgesics for 24 h prior to the testing session. Healthy controls were also asked not to take any analgesic medication 24 h prior to the pain testing.

The pain testing equipment was demonstrated and explained using a "scripted" text. A few discrete pressure stimuli were applied to familiarize subjects with the procedure. The instructions for the different tests also followed a standardized script and additional information and explanations were provided if required. The sequence of testing was the same for all subjects.

2.3. Pressure pain testing

A dolorimeter exam at the 18 defined tender points, and four control points (the bilateral thumbs and anterior tibial muscles) was performed on all subjects (Wolfe et al., 1990) using a 3.14 cm^2 footplate size. Pressure was increased at a rate of 1 kg/s and subjects were instructed to indicate when they first perceived pain. If no pain response was elicited up to 12 kg of pressure, this value was recorded as the pain threshold. The average pressure pain threshold for all 18 tender point sites was calculated and expressed as kg/3.14 cm^2.

Discrete pressure stimuli were applied using a remote stimulation device to eliminate any direct examiner/subject interaction. The apparatus induced pressure with a hydraulic system in which a 1 cm^2 hard rubber circular probe was pressed against the left or right thumbnail (see below). The thumbnail was chosen as it has been shown to be more sensitive to pressure in FM subjects than in HC (Petzke et al., 2001), and remains a "neutral" point for patients with FM compared to a typical tender point. The stimulator was positioned over the thumb by a plastic housing and the hydraulic system activated by calibrated weights placed on a moveable table. Valves controlled stimulus timing. The combination of valves and calibrated weights produced controlled, repeatable stimulation that approached a rectangular waveform.

To compare the effect of stimulus presentation on unpleasantness and intensity ratings, both an ascending and a random series were performed on each subject.

2.3.1. Discrete ascending pressure

For the ascending series (ASC), discrete stimuli of 5 s duration were applied to the right thumbnail. Initial stimulation pressure was 0.45 kg and stimulation pressure was increased in 0.45 kg increments up to either a subject's level of pain tolerance or a maximum of 9.1 kg. Subjects used two 21-box numerical descriptor scales to rate the intensity and then the unpleasantness of sensations evoked by each stimulus (see Fig. 1). After subjects had rated a stimulus with a pain intensity of greater than 10 (mild to moderate pain), they were asked if they wished to continue after each succeeding stimulus. Inter-stimulus interval was 30 s.

2.3.2. Discrete random pressure

For the random series (RAN), subjects were instructed that they would receive a different series of stimuli within the range of the previous ascending series. If tolerated, seven stimuli (0.45, 0.91, 1.36, 1.82, 2.73, 3.64, 4.54 kg) were twice presented in random order to the left thumb and ratings of sensory intensity and unpleasantness were obtained using the 21-box scales. Four subjects with FM received less than the seven stimuli (1 only four stimuli, and 3 only 6 stimuli). In both patients and controls this weight distribution resulted in at least three values between pain threshold and tolerance. Inter-stimulus interval was 30 s.

2.4. Pain intensity and unpleasantness estimation

Pain intensity and unpleasantness ratings in response to discrete stimuli were recorded on two separate 21-box numerical descriptor scales (Fig. 1) using standardized instructions, similar to Price et al. (1984). These scales

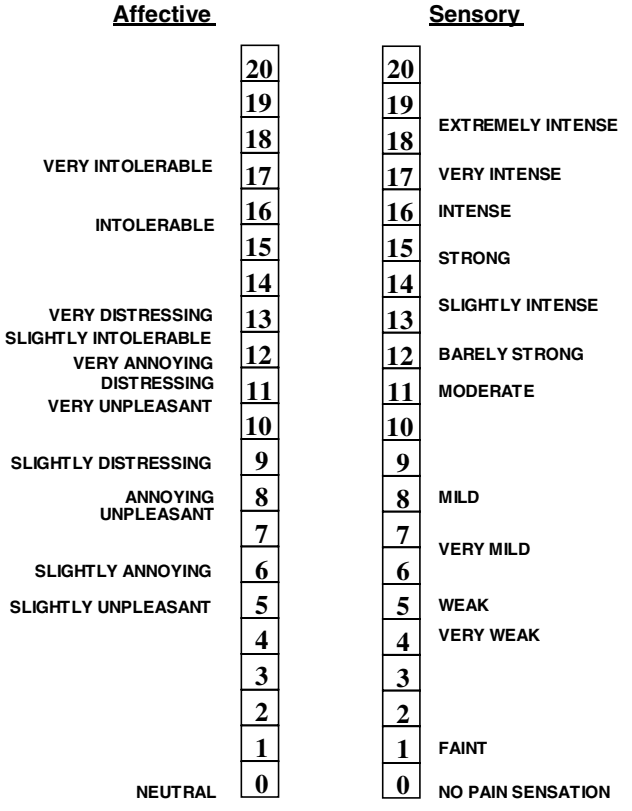

Fig. 1. Affective and sensory numerical descriptor scales used to measure evoked pain dimensions of affective unpleasantness and sensory intensity.

had been constructed from previously quantified verbal descriptors (Gracely et al., 1978a,b, 1979). They posses logarithmic properties with regard to the spacing of the descriptors, and had been shown to be sensitive in other studies (Eliav and Gracely, 1998; Sternberg et al., 1998; Gracely et al., 2002; Lembo et al., 2000; Petzke et al., 2003a).

In addition to the two 21-box scales described above, experimental pain was also assessed with the Short Form of the McGill pain questionnaire (MPQ:SF). Subjects were asked to rate the worst pain experienced during the two prior testing sessions (ASC; RAN). Thus the subjective ratings were not in response to a specific stimulus but reflected the retrospective perception and experience during the two evoked pain paradigms.

2.5. Questionnaires

2.5.1. Functional status

The SF-36, is a brief, well-established, self-administered patient questionnaire for the assessment of health status (Ware et al., 2000). The SF-36 measures eight domains of health status, and summary physical (PCS) and mental health (MCS) scales can be calculated by combining and weighting the various individual scales. These summary scales are standardized to have a mean = 50, SD = 10 in the general US population (Ware and Kosinski, 2001).

2.5.2. Depressive symptoms

Neurovegetative and cognitive symptoms of depression were evaluated by the Beck Depression Inventory (BDI), a 21-item measure of the severity of current depressive symptoms that has been validated for use in rheumatic diseases (Burckhardt et al., 1994).

2.5.3. Distress

The Brief Symptom Inventory (BSI) was used to obtain an indicator of distress (Derogatis and Spencer, 1983). This 51-item instrument contains nine sub-scales and a Global Severity Index (GSI), which was used as a general measure for distress; the anxiety sub-scale was used to measure an individual's anxiety.

2.5.4. Clinical pain

Clinical pain was assessed by the Short Form of the McGill pain questionnaire (MPQ:SF). This 15-item inventory yields both a sensory and affective subscale (Melzack, 1987). Scores were expressed as % of the maximum possible score for each dimension (Stohler and Kowalski, 1999).

2.6. Statistical analysis

Statistical analyses were performed in several stages: (1) Descriptive statistics defining similarities and differences between the FM and healthy control groups, (2) Analyses comparing pain intensity and unpleasantness between the FM and HC groups in the ASC and RAN series of tests, (3) Analyses comparing the relative unpleasantness between the FM and HC groups, (4) Analyses addressing the influence of differences in mean pain intensity between the two groups on the relative unpleasantness, (4) Analyses exploring associations between relative unpleasantness and affective symptoms, and (5) the relative unpleasantness of clinical compared to evoked pain in patients with FM.

2.6.1. Comparison of pain intensity and unpleasantness

To compare responses in the discrete pressure testing paradigms (ASC, RAN), the areas under the stimulus response curve (AUC) for pain intensity and unpleasantness for the 0.45–4.5 kg stimulus range were calculated for both groups. Since the curve was defined as a set of stimulation pressures (x_i) and corresponding pain ratings (y_i), the AUC was calculated as follows: $\mathrm{AUC} = \sum(((y_{(i+1)} + y_i)/2) \times (x_{(i+1)} - x_i))$. The sum included all available data points in a given stimulus range. In subjects who could not complete the whole testing range the highest pain intensity or unpleasantness rating was substituted for the missing values (only six values in four FM subjects).

2.6.2. Relative unpleasantness

Relative unpleasantness is typically defined as the ratio of unpleasantness to intensity ratings (unpleasantness/intensity; (Rainville et al., 1992)). Since the box scales we used possess logarithmic properties (Gracely et al., 1978a), relative unpleasantness was calculated as the difference of unpleasantness minus intensity, which corresponds to a ratio in arithmetic units. We calculated the mean relative unpleasantness as the AUC for unpleasantness ratings minus the AUC for intensity ratings.

Relative unpleasantness for clinical and evoked pain ratings with the MPQ:SF in patients with FM was also calculated. The respective MPQ:SF % scores were used as follows: %affective score/%sensory score.

2.6.3. Mean perceived pain intensity and range restriction

The restriction of stimulus intensity to a range from 0.45 to 4.5 in ASC and RAN was necessary to allow the comparison of the average group responses. With respect to the relationship between ratings of pain intensity and unpleasantness in the two groups, this range restriction could result in a scaling bias due to the group difference in pain sensitivity, with FM patients typically using higher scale values than HC. Therefore the mean perceived pain intensity was calculated for ASC and RAN and correlated with the respective relative unpleasantness.

To assess the use of the unpleasantness and intensity scales across the whole individual rating range of the AUCs, the relative unpleasantness and the mean perceived pain intensity were also calculated for all available responses in the ascending paradigm up to individual tolerance or the stimulus maximum of 9.1 kg (ASC-TOL) in both groups.

2.7. Statistical procedures

t-Tests and χ-square tests were used to characterize the demographic (e.g. age, sex,), clinical pain characteristics (menstrual status, disease duration, MPQ:SF pain scores, tender point and dolorimetry scores), and affective measures (BDI, BSI). ANOVAs were used to evaluate whether unpleasantness or relative unpleasantness differed between groups and across pain-evoking paradigms. Correlational analyses were used to explore associative relationships between relative unpleasantness and mean perceived pain intensity, and affective variables. All data are expressed as mean ± SEM unless stated otherwise. Data analysis was performed with SPSS 11.0 and MS Excel.

3. Results

3.1. Subjects

The 43 clinic patients included in the study fulfilled the ACR criteria for FM on the day of testing. Subjects were age and gender matched with 28 healthy control subjects (Table 1). The observed slight difference in age was not statistically significant ($p = 0.26$) nor was the proportion of males to females ($p = 0.75$). Distribution of menstrual status in the two groups was similar: 62% of patients and 50% of controls were postmenopausal; cycle stages in the remaining subjects were evenly distributed between the two groups and not statistically significantly different (χ-square $p = 0.29$). Not surprisingly, FM subjects displayed statistically significant greater clinical pain scores (MPQ:SF), depression, distress, and tenderness compared to controls. Only four of the healthy controls had more than four positive tender points on manual palpation.

3.2. Pressure thresholds – dolorimetry on thumb and tender points

As expected, all pressure pain thresholds were significantly higher in the control subjects than in the FM patients (Table 1; 8.5 ± 0.35 vs. 4.5 ± 0.2 kg/cm^2 for tender points; 10.0 ± 0.4 vs. 6.1 ± 0.4 kg/cm^2 for right thumb; 10.6 ± 0.4 vs. 6.1 ± 0.4 kg/cm^2 for left thumb; all $p < 0.0001$). Within the groups, measures at the thumbs and tender points were highly inter-correlated; more so in the patient group ($r = 0.73$–0.93; all $p < 0.0001$) than in the controls ($r = 0.54$–0.73; all $p < 0.003$) possibly due to range restriction in the latter group.

3.3. Unpleasantness and pain intensity

3.3.1. ASC

Patients with FM had higher AUC summary ratings than healthy controls for both unpleasantness and pain intensity in the ascending paradigm (Fig. 2(a)). A 2 × 2 ANOVA of group X pain dimension revealed significant main effects for group (FM > HC, $F[1,69] = 30.3$, $p < 0.001$) and dimension (Unpleasantness > Intensity, $F[1,69] = 5.1$, $p < 0.03$), but no significant interaction ($F[1,69] = 0.9$, $p = 0.35$). This indicated that the difference between unpleasantness and intensity within both groups was similar.

3.3.2. RAN

Similar to the ASC paradigm, patients with FM had an increased AUC for unpleasantness and intensity compared to HC for RAN (Fig. 2(b)). A 2 × 2 ANOVA

Table 1
Clinical characteristics of the two subject groups: age, male/female ratio, average subject questionnaire responses, and standard pain measures (mean ± SDV)

	Fibromyalgia patients, $N = 43$	Healthy controls, $N = 28$	p
Age (years)	49.7 ± 11.7	46.8 ± 9.5	n.s.
Male (N)/Female (N)	4/39	2/26	n.s.
Disease duration (years)	10.5 ± 8.0	–	–
Regional pain score	40.9 ± 16.8	1.1 ± 0.4	0.0001
MPQ:SF – total score	18.3 ± 8.2	0.4 ± 0.1	0.0001
MPQ:SF – sensory score	14.7 ± 6.1	0.4 ± 0.1	0.0001
MPQ:SF – affective score	3.8 ± 3.1	0.0 ± 0.0	0.0001
BSI Global Severity Index	63.8 ± 1.4	46.2 ± 1.9	0.0001
BDI	15.3 ± 10.1	2.7 ± 0.6	0.0001
Manual tender point count	14.3 ± 0.34	2.1 ± 0.57	0.0001
(range)	[11–18]	[0–8]	
Dolorimetry pain threshold (kg/3.14 cm^2)	4.47 ± 0.22	8.55 ± 0.35	0.0001

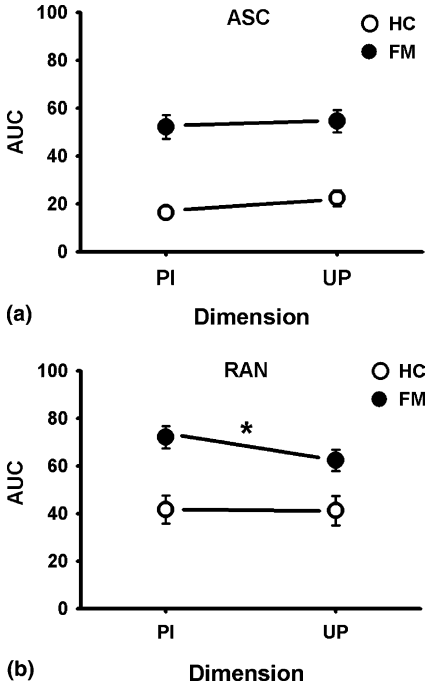

Fig. 2. Pain intensity (PI) and unpleasantness (UP) ratings for FM and HC expressed as area under the curve (AUC) ±1 SEM. (a) ASC – The FM group displayed greater PI and UP compared to HC (PI = 52.1 ± 4.99 FM, 16.3 ± 2.36 HC; UP = 54.5 ± 4.70 FM, 22.3 ± 3.28 HC), however there was no significant interaction. (b) RAN – Similar to the ASC paradigm, the FM group had greater PI and UP compared to HC (PI = 72.04 ± 4.62 FM, 41.6 ± 5.91 HC; UP = 62.3 ± 4.56 FM, 41.2 ± 6.17 HC). However within groups, FM subjects displayed less UP than PI as compared to HC (* significant interaction).

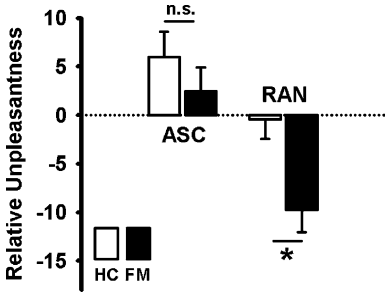

Fig. 3. Relative unpleasantness (AUC for UP minus AUC for PI) ±1 SEM in the two paradigms: For ASC a student's *t*-test revealed no significant difference ($p = 0.35$) between FM (2.44 ± 2.48) and HC (5.96 ± 2.62). However for RAN, relative unpleasantness was significantly less for FM as compared to HC (RAN: $*p < 0.007$, −9.75 ± 2.33 FM, −0.41 ± 2.05 HC).

of RAN group X pain dimension revealed significant main effects for group (FM > HC, $F[1,69] = 12.5$, $p < 0.001$) and pain dimension, however the dimension effect was reversed in direction (unpleasantness < intensity, $F[1,69] = 9.3$, $p < 0.003$) as compared to the ASC paradigm. A significant group X dimension interaction ($F[1,69] = 7.9$, $p = 0.007$) was detected indicating that the difference between unpleasantness and intensity ratings within the FM group differed from the HC group.

3.4. Relative unpleasantness

The difference in degree and direction of the interaction between group X pain dimensions seen in Fig. 2 is explained by Fig. 3, which shows the relative unpleasantness for ASC and RAN. Patients with FM displayed generally less relative unpleasantness and this difference was significant and pronounced in the random paradigms ($p < 0.01$).

We compared relative unpleasantness in ASC and RAN using a 2 × 2 ANOVA to analyze the effect of pain testing methodology. A significant main effect for group was observed (FM < HC: $F[1,69] = 4.0$, $p < 0.05$). The effect of method (ASC > RAN) was also highly significant ($F[1,69] = 37.8$, $p < 0.0001$), while the group-method interaction approached significance ($F[1,69] = 3.7$, $p = 0.06$). These findings indicate (1) that both patients with FM and HC described equally intense pain sensations as more unpleasant in the ascending paradigm compared to the less predictable random paradigm, (2) that this difference between paradigms is more pronounced in patients with FM and (3) that patients with FM report generally less relative unpleasantness than HC.

The above data indicated that with random stimulus presentation, despite overall higher pain and unpleasantness ratings than HC, FM patients had relatively less unpleasantness compared to HC. This can also be visualized by plotting the mean unpleasantness score versus the mean pain intensity score for all pressures eliciting a painful sensation (mean pain intensity score >0.5 representing faint pain) in the ASC (Fig. 4(a)) and RAN paradigms (Fig. 4(b)). Mean scores in the ascending paradigm showed a similar linear pattern in both groups, with the FM curve shifted towards higher values. However, FM mean scores in the random paradigm consistently trended toward lower values along the affective dimension, suggesting an additional parallel downward shift in relative unpleasantness over the whole stimulus–response curve.

Affective and sensory sub-scale scores of evoked experimental pain were also compared using the MPQ:SF. Similar to the above findings, subjects with FM reported relatively less evoked affective pain as measured by the MPQ:SF (Fig. 5: Evoked pain in HC and FM). Although the sensory scores were significantly higher (FM > HC; $p < 0.05$), the affective scores were not statistically different ($p = 0.29$). Thus, a combination of a different scale and a retrospective assessment also showed that the relative unpleasantness of evoked pain was again less for the FM subjects (i.e. identical unpleasantness for an increased sensory intensity).

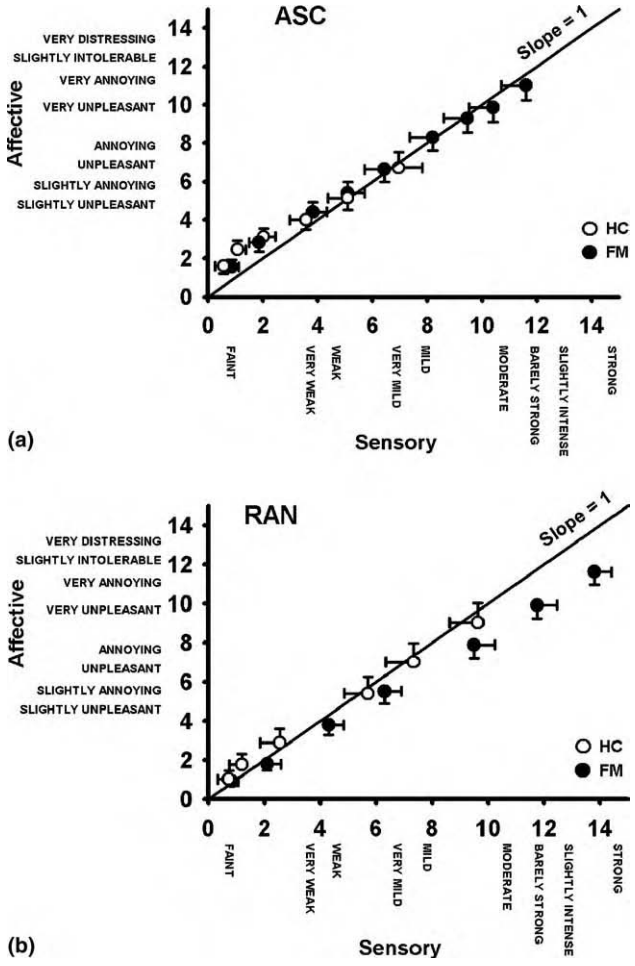

Fig. 4. Affective versus sensory plots: (a) ASC – 21-box scale mean values ±1 SEM for affective and sensory ratings for 0.91, 1.36, 1.82, 2.27, 2.73, 3.18, 3.64, 4.09, and 4.54 kg weights in FM and 2.27, 2.73, 3.18, 3.64, 4.09, and 4.54 kg weights in HC, representing stimuli inducing an average pain intensity rating >0.5 (faint pain). FM subjects tend to greater affective and sensory scores but show a similar stimulus-response curve. (b) RAN – 21-box scale mean values ±1 SEM for affective and sensory ratings in both groups for 0.45 (not in HC), 0.91, 1.36, 1.82, 2.73, 3.64, and 4.54 kg weights, representing stimuli inducing an average pain intensity rating >0.5 (faint pain). FM subject means tended toward lower affective and greater sensory scores resulting in a parallel downward shift of the stimulus–response curve.

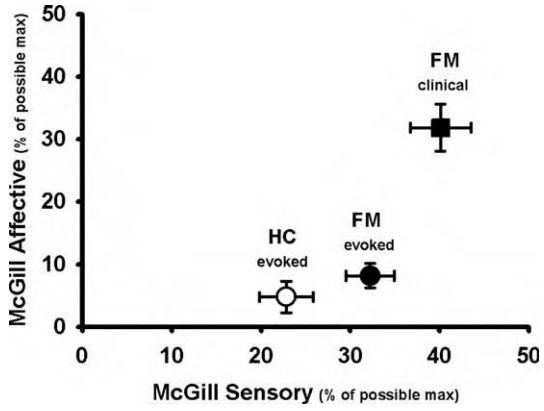

Fig. 5. Retrospective ratings of experimental pressure pain (for HC and FM) and clinical pain (for FM only) using the MPQ:SF affective and sensory sub-scales, expressed as % of possible maximum score. FM and HC evoked pain: The sensory mean was greater in FM than HC ($p < 0.05$: 32.2 ± 2.72 FM, 22.8 ± 2.98 HC), however the affective scores were not significantly different ($p = 0.29$: 8.14 ± 1.95 FM, 4.76 ± 2.55 HC). FM evoked and clinical pain: FM patients reported more sensory and affective clinical pain, with more relative unpleasantness compared to the evoked pain.

3.5. Correlation of relative unpleasantness with mean perceived pain intensity

A significant effect of the pain testing methods on relative unpleasantness was found for both groups, with higher relative unpleasantness ratings in the ascending series (Fig. 3). However, overall ratings of unpleasantness and pain intensity were higher in the random than in the ascending paradigms for both groups (Figs. 2 and 4(a) and (b)). Therefore we examined the relationship between mean perceived pain intensity and relative unpleasantness for both FM and HC subjects (Table 2). The relative unpleasantness for patients with FM correlated negatively with perceived pain intensity in the ASC and RAN paradigm, while HC displayed a similar but non-significant trend. This negative correlation, however, was significant for both groups in ASC-TOL when the entire stimulus range that was delivered during the ascending paradigm was evaluated. This relationship is also evident in Figs. 4(a) and (b) if the position of pressure stimuli in both groups is compared to the bisecting line (indicating equal pain intensity and unpleasantness). In Fig. 4(a), stimuli inducing higher pain intensity ratings generally lie below this line (indicating less relative unpleasantness) while stimuli inducing lower pain intensity are positioned above (indicating more relative unpleasantness). In Fig. 4(b) the same relationship is seen, however, patients with FM reported generally less unpleasantness resulting in a parallel and downward curve shift (see above).

The combination of the restriction of the stimulus range in the ASC and RAN paradigms and the negative correlation of relative unpleasantness with pain intensity may have contributed to the differences in relative unpleasantness observed between patients with FM and HC, but it fails to explain the increasing group differences in relative unpleasantness in the random paradigms with overall higher pain intensity and unpleasantness ratings.

3.6. Correlation with psychometric measures

We examined the interaction of relative unpleasantness with the psychological constituents of each subject to determine if psychological parameters could account for the differences observed above. The

Table 2
Correlation between relative unpleasantness and mean perceived pain intensity in the three paradigms, and ASC-TOL for both patients with FM and HC

		Relative unpleasantness					
Mean perceived		ASC		RAN		ASC- TOL	
Pain intensity		HC	FM	HC	FM	HC	FM
ASC	r	−0.11	−0.39	–	–		
	p	0.56	0.009	–	–		
RAN	r	–	–	−0.23	−0.26		
	p	–	–	0.24	0.09		
ASC-TOL	r					−0.37	−0.35
	p					0.05	0.02

Table 3
Correlation between relative unpleasantness in the three paradigms, ASC-TOL and psychometric measures of distress (BSI-GSI), anxiety (BSI-subscale), depression (BDI), and clinical pain (MPQ:SF affective and sensory)

		Relative unpleasantness			
		ASC		RAN	
		HC	FM	HC	FM
BSI-Anxiety	r	−0.18	−0.14	0.1	0.01
	p	0.37	0.37	0.62	0.96
BSI-GSI	r	0.05	0.1	0.13	0.18
	p	0.81	0.55	0.51	0.26
BDI	r	0.06	0.03	−0.10	0.17
	p	0.76	0.85	0.63	0.29
MPQ:SF – Total score	r	0.03	0.002	−0.2	0.05
	p	0.87	0.98	0.32	0.77
MPQ:SF – Sensory score	r	0.03	−0.01	−0.2	−0.02
	p	0.87	0.98	0.32	0.92
MPQ:SF – Affective score	r	n.a.[a]	0.01	n.a.[a]	−0.01
	p		0.52		0.97

[a] All HC had a MPQ:SF affective score of 0.

correlation coefficients for the relationships between relative unpleasantness in the ASC and RAN paradigms and psychometric measures for anxiety, distress, depression, and clinical pain are shown in Table 3. None of the correlations were significant in either group.

3.7. Evoked and clinical pain

The MPQ:SF provides the opportunity to compare pain dimensions in both clinical and evoked settings within the FM group (Fig. 5). For the FM subjects alone a 2×2 ANOVA showed significant main effects for type of pain (clinical > experimental, $F[1,42] = 76.4$, $p < 0.0001$), pain dimension (sensory > affective, $F[1,42] = 138.4$, $p < 0.001$), and a highly significant interaction ($F[1,42] = 68.0$, $p < 0.0001$). Relative unpleasantness was 0.83 ± 0.09 for clinical but only 0.23 ± 0.05 for evoked pain ($p < 0.0001$). These results indicated that clinical pain was more unpleasant than experimental pain of a given sensory intensity.

4. Discussion

This study examined two dimensions of pain, intensity and unpleasantness, in both FM and HC subjects. The primary finding from this investigation of noxious pressure was that patients with FM reported greater pain intensity but less relative unpleasantness as compared to healthy controls. These results suggest that although FM patients experience clinical pain on a regular basis, they are less bothered by pain in experimental settings. This difference may be explained by multiple factors, which may not be mutually exclusive.

4.1. Why do FM subjects display relatively less unpleasantness?

FM patients experience pain of a significant magnitude for a prolonged duration of time. The mean duration of the disease for patients in this study was 10.5 years. Therefore the stimuli used in these experiments might be perceived as relatively less unpleasant due to

the fact that FM patients are simply more familiar with painful sensations than controls. A similar explanation could be that because the FM patients have already experienced clinical pain unpleasantness of significant magnitude, they compare the evoked stimuli to their greater clinical pain. Indeed in this study the FM subjects using the MPQ:SF reported their clinical pain as more unpleasant than evoked pain of similar intensity (Fig. 5). This effect seen in clinical pain subjects was predicted by Rollman and was termed adaptation (Rollman, 1979, 1983). He reasoned that subjects use their clinical pain as a reference point for pain in experimental settings. In contrast, this reference framework may be missing in the control subjects.

In addition to an adaptation effect operating during the evaluation and rating of pain experience, it is also possible that the relative unpleasantness observed with FM may reflect modulation by intrinsic mechanisms activated by persistent pain. For example, several studies have found that endogenous analgesic systems can be activated in healthy controls but not in patients with FM (Kosek et al., 1996; Lautenbacher and Rollman, 1997; Staud et al., 2003). Although often interpreted as a disorder in intrinsic analgesia, this result is also consistent with a state in which the persistent pain of FM results in maximal tonic activation of endogenous analgesic systems (Gracely et al., 2003), and that the reduction in relative unpleasantness observed with FM reflects preferential modulation of pain unpleasantness. Neither the adaptation nor this modulation mechanism needs to be mutually exclusive and both mechanisms could contribute to our results.

4.2. Why does random presentation differ from ascending?

An interesting finding in this study was that differences in relative unpleasantness were detected only when the painful stimuli were presented in a random fashion. When the stimuli were presented in a predictable ascending fashion there was no group X pain-dimension interaction. Some of this difference might be explained by the generally higher pain ratings from FM patients for a given stimulus intensity and the trend to less relative unpleasantness with higher pain ratings in both groups (Table 2 and Fig. 4(a) and (b)). But the similar linear pattern of mean pain intensity and unpleasantness ratings of ascending pressure stimuli present in both groups (Fig. 4(a)), is contrasted by a parallel downward shift in unpleasantness ratings in patients with fibromyalgia in response to randomly presented stimuli (Fig. 4(b)). Thus, mechanisms other than the properties and range restriction of the pain scales likely mediate the observed difference in relative unpleasantness.

The cognitive context of the random and ascending paradigms are clearly different. In the ascending paradigm, subjects know that the intensity of the next stimulus will be just slightly greater than the intensity of the preceding stimulus. In contrast, the unpredictable quality of the random presentation results in a state of uncertainty that may lead to exaggerated responses. Unpredictable painful stimuli have been previously shown to be more unpleasant than anticipated painful stimuli (Price et al., 1980) and even non-painful stimuli appear more unpleasant when presented in a random fashion (Sawamoto et al., 2000). Our finding that ratings of both intensity and unpleasantness were higher in the random than the ascending series in both groups (Fig. 2) is consistent with these previous results. At this point it is important to realize that patients with FM were even less inclined than HC to respond in an exaggerated fashion, showing less relative unpleasantness in the random paradigm and that this relative unpleasantness was not correlated to any of the psychosocial or clinical pain measures.

It is also conceivable that the difference between the ascending and random paradigms reflects the effects of task demands in the ascending methods. Subjects know that the stimulus intensity increases on successive trials, and thus likely adapt a response behavior in which successive responses also increase. This potentially produces results that are automatically monotonic with stimulus intensity. Subjects can produce such data without even attending to the stimulus (Gracely et al., 2003). This is an example of a "stimulus-independent bias".

These data reinforce the notion that the manner in which painful stimuli are presented can profoundly influence how pain is reported. Pain report is not simply dependent upon the subject, but involves an interaction between the subject, experimenter, and paradigm.

4.3. What is the relevance of this difference?

This question is complicated by the fact that pain is a multidimensional sensation. One measure may detect more of the sensory components of pain (i.e. intensity, timing, or location) whereas another may be more sensitive to the emotional or affective dimension. Indeed different clinical interventions appear to differentially alter the sensory and affective components of pain (for review (Fernandez and Turk, 1992) therefore it seems logical that experimental paradigms may elicit different dimensions of the pain sensation as well.

Evidence suggests that the random protocol is less biased by affective and evaluative factors such as subject hypervigilance or expectancy, and stimulus-independent bias (Gracely et al., 2003). In contrast, ascending pain paradigms such as the dolorimeter and tender point count correlate more with a subject's psychological state (Petzke et al., 2003b). Again this may play into the

"known" or expectant property of the ascending paradigms as compared to the "unknown" random paradigms. Subjects know that the succeeding stimulus will be more intense in the ascending paradigms and therefore may react differently to it. Evidence in support of this hypothesis is presented here, where the relative unpleasantness was significantly more in the ascending paradigms than in the random paradigms for both groups (Fig. 3). This suggests that the ascending paradigm evokes a greater affective magnitude than the random paradigm. This is somewhat counterintuitive, in that as noted above the ratings for both intensity and unpleasantness were higher in the random paradigm than for the ascending, yet only the ascending paradigms are related to measures of mood and distress (Petzke et al., 2003b). These data suggest that other psychological constructs, perhaps related to control, are driving symptom report and lowering of pain ratings obtained during ascending paradigms, and that these constructs affect both healthy controls and patients with fibromyalgia in a similar manner.

5. Conclusion

The dimensions of pain intensity and unpleasantness are separate yet highly correlated. Results presented here further support this hypothesis and in addition suggest that the presence of a chronic pain state can alter one's response to evoked pain. Indeed Rollman reasoned that chronic pain subjects may display a different "adaptation-level" than normal subjects based on differences in their "internal comparison" mechanisms of pain stimuli (Rollman, 1979). As noted above FM subjects may compare the experimental pain to their more intense clinical pain and therefore rate the evoked sensations as less unpleasant.

Results presented here are consistent with those obtained from other chronic pain states such as cancer and causalgia (Price et al., 1987). In general clinical pain is perceived as more unpleasant than experimentally evoked sensations of similar magnitude. This raises the hypothesis that differing chronic pain conditions may elicit similar changes in evoked pain perceptions, however uncovering the underlying mechanisms will require further research.

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A twin study of posttraumatic stress disorder symptoms and chronic widespread pain

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Abstract

Previous studies of the association between posttraumatic stress disorder (PTSD) and chronic widespread pain (CWP) or fibromyalgia have not examined the role of familial or genetic factors. The goals of this study were to determine if symptoms of PTSD are related to CWP in a genetically informative community-based sample of twin pairs, and if so, to ascertain if the association is due to familial or genetic factors. Data were obtained from the University of Washington Twin Registry, which contains 1042 monozygotic and 828 dizygotic twin pairs. To assess the symptoms of PTSD, we used questions from the Impact of Events Scale (IES). IES scores were partitioned into terciles. CWP was defined as pain located in 3 body regions lasting at least 1 week during the past 3 months. Random-effects regression models, adjusted for demographic features and depression, examined the relationship between IES and CWP. IES scores were strongly associated with CWP ($P < 0.0001$). Compared to those in the lowest IES tercile, twins in the highest tercile were 3.5 times more likely to report CWP. Although IES scores were associated with CWP more strongly among dizygotic than among monozygotic twins, this difference was not significant. Our findings suggest that PTSD symptoms, as measured by IES, are strongly linked to CWP, but this association is not explained by a common familial or genetic vulnerability to both conditions. Future research is needed to understand the temporal association of PTSD and CWP, as well as the physiological underpinnings of this relationship.

Keywords: Chronic widespread pain; Fibromyalgia; Genetic; Posttraumatic stress disorder; Twins

1. Introduction

Chronic widespread pain (CWP) is a common problem in the general population, with an estimated prevalence ranging from 7% to 13% across different countries (Neumann and Buskila, 2003). The American College of Rheumatology defines CWP as pain present in at least 2 contra-lateral body quadrants and the axial skeleton that has persisted for at least 3 months (Wolfe et al., 1990). Many experts believe that both CWP and fibromyalgia (FM), a severe subtype of CWP, represent one end of the spectrum of musculoskeletal pain disorders (Croft et al., 1996; Wolfe, 1997; Croft, 2000). CWP has a modest female predominance and its prevalence increases with age (Hunt et al., 1999; Buskila et al., 2000; Bergman et al., 2002). People with CWP also

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experience poor subjective health, fatigue, sleep disruption, and physical impairments (Prescott and Jacobsen, 1993; Aaron et al., 2002). Despite a growing body of literature, the etiology and pathophysiology of CWP remain poorly understood. Recently, several studies have documented that CWP and FM are strongly associated both with the symptoms of posttraumatic stress disorder (PTSD) (Walter et al., 1998; Wolfe and Skevington, 2000; White et al., 2002) and with the clinically diagnosed disorder itself (Benedikt and Kolb, 1986; Benjamin et al., 2000; Cohen et al., 2002; Roy-Byrne et al., 2004). Conversely, high rates of CWP and FM also have been observed among persons with PTSD (Amir et al., 1997; Dobie et al., 2004; Raphael et al., 2004).

Clinic-based studies have shown that PTSD and CWP, persistent pain, or FM were strongly associated, but the link was potentially attributable to the biases inherent in using clinical samples (Crook et al., 1989; Aaron et al., 1996; Macfarlane et al., 1999). Results from population-based studies, however, have substantiated both the existence and the strength of the association (Benjamin et al., 2000; Buchwald et al., 2005). Additionally, both PTSD and FM are thought to be partially heritable. Family studies have shown that FM aggregates strongly in families (Pellegrino et al., 1989; Buskila et al., 1996; Buskila and Neumann, 1997; Arnold et al., 2004), but linkage studies have found either a weak linkage or none at all (Yunus et al., 1999; Gursoy, 2002). Investigations into the heritability of PTSD have shown that PTSD is related to family history of psychiatric illness (Davidson et al., 1989; Koenen et al., 2002; Koenen et al., 2003).

No previous investigation has controlled for genetic or environmental influences on the relationship between PTSD and CWP. This study addresses some of these limitations by examining the association of PTSD and CWP in a sample of twins enrolled in a community-based registry in Washington State. In these analyses, we address the following questions: (1) Are the symptoms of PTSD and CWP associated? If so, (2) Do familial/genetic factors account for the association of PTSD symptoms and CWP?

2. Methods

2.1. Sample

The University of Washington Twin Registry is a community-based sample of twins derived from the drivers' license applications of the Washington State Department of Licensing. Unique to Washington State, drivers' license numbers are derived from a person's last name, first and middle initials, and date of birth. In the past, this led to the issuance of duplicate drivers' license numbers. Hence the Department of Licensing began asking every new applicant if he or she is a member of a twin pair to avoid issuing duplicate license numbers to twins. Because Washington State agencies are permitted by law to share data, the Department of Licensing has provided a list of all new drivers' license applicants who are twins to the University of Washington since 1998. Upon receiving the names from the Department of Licensing, the University of Washington Twin Registry staff sends each twin an invitation to join, a brief survey to complete, and an incentive. If the twin does not respond within one month, a second invitation and survey are mailed. The co-twin is mailed a survey using contact information provided by the index twin. To date, the University of Washington Twin Registry has enrolled 1042 monozygotic (MZ) pairs, 828 dizygotic (DZ) pairs, and 121 pairs of undetermined zygosity. The University of Washington Human Subjects Review Committee approved the procedures for establishing the twin registry and all data collection involved in this study. Informed consent was obtained from all participants.

2.2. Survey

The survey contains items on socio demographics, symptoms, physician-diagnosed health conditions including PTSD and depression, habits, health care use, and abridged psychiatric measures, such as the Impact of Events Scale (IES) (Horowitz et al., 1979) and a modified version of the London Fibromyalgia Epidemiology Study Screening Questionnaire (White et al., 1999).

2.2.1. Zygosity assignment

As part of the mailed questionnaire all twins were asked questions about childhood similarity to assess zygosity. Studies have shown that questions about childhood similarity in twin pairs can be used to correctly classify zygosity with an accuracy of 95–98%, in comparison with zygosity determined by biological indicators (Torgersen, 1979; Eisen et al., 1989). The following questions were asked: "As children were you and your twin as alike as 2 peas in a pod or of ordinary family resemblance?" and "When you were children how often did [parents, other relatives, teachers, strangers] have difficulty in telling you apart?" The responses to these similarity questions were then used in a multi-step process to assign zygosity.

2.2.2. Sociodemographic factors and clinical conditions

Sociodemographic factors collected in the survey included age, race, gender, education, and marital status. Age was calculated from the year of birth. The twins were asked if they were White, Black, Asian/Pacific Islander, Native American, Hispanic/Latino, or other. We dichotomized responses to White or other. Marital status was assessed by asking the twin whether he or she was currently single, never married, living with a partner, married, separated, divorced, or widowed. This variable was dichotomized to married or other. For education, we asked about the highest level of education completed (kindergarten to graduate school). One question inquired about a physician diagnosis of depression and another about a physician diagnosis of PTSD. Because studies have shown body mass index and depression to be strongly associated with CWP and FM (McBeth et al., 2001; Yunus et al., 2002) as well as with PTSD (Solter et al., 2002; Karlovic et al., 2004), these variables were included as covariates in the regression models to adjust for their potentially confounding effects.

2.2.3. Posttraumatic stress disorder symptoms

PTSD is a disorder in which an overwhelming traumatic event results in intense fear, helplessness, horror, and avoidance of stimuli associated with the trauma (American Psychiatric Association, 1994). PTSD symptoms were identified by using the IES, which assesses current subjective distress resulting from a stressful life event. Because individuals with PTSD are often reluctant to seek evaluation and treatment (Amaya-Jackson et al., 1999), we did not use the self-report of a physician diagnosis of PTSD. The IES captures qualities of conscious experience that encompass stressful life events, such as bereavement or personal injuries from accidents, violence, illness, or surgery (Horowitz et al., 1979). Although the IES is a measure only of the DSM-IV intrusion and avoidance symptom criteria for PTSD (American Psychiatric Association, 1994), previous studies have shown the IES to be strongly correlated with a diagnosis of PTSD. For example, a Dutch study of pain and stress in burn victims found that IES scores >26 were indicative of serious PTSD (Taal and Faber, 1997). As a screening measure for PTSD, the sensitivity of the IES ranges from 0.94 to 1.00 and the specificity ranges from 0.78 to 0.84 (Wohlfarth et al., 2003). More recently, it has been suggested that additional items on hyper-arousal could be added to the IES (Weiss and Marmar, 1997).

We used 11 of the 15 original IES items, deleting 4 of the original items based on the cluster analysis that was conducted by the developers of the IES. These items had the poorest correlation with the IES intrusion and avoidance subscales (Horowitz et al., 1979). Internal reliability of the IES was assessed by using Cronbach's alpha and validity was evaluated by its concordance with a self-report of PTSD diagnosed by a physician. For the 11 IES items used in this analysis, the Cronbach's alpha was 0.90, indicating a high degree of internal consistency. Likewise, the validity of the IES was demonstrated by a strong trend between the IES and a physician diagnosis of PTSD ($X^2_{\text{trend}} = 59.3, P < 0.0001$).

Each IES item has 4 response categories (0, not at all; 1, rarely; 3, sometimes; 5, often). These values are summed to create an overall score (range 0–55). We grouped the scores into terciles representing increasing levels of current subjective distress: 0–6 (lowest distress), 7–24 (moderate distress), and 25+ (highest distress). We included only twins who answered at least 6 of the 11 IES items, and as previously recommended, missing values were imputed by using the respondent's average score across completed items (Ware et al., 1980). For example, if a twin did not answer 2 IES items, we used the mean score across the 9 completed items to impute values for the missing items.

2.2.4. Chronic widespread pain

The survey included 3 of 4 questions about CWP adapted from the self-report form of the London Fibromyalgia Epidemiology Study Screening Questionnaire (White et al., 1999). Our questions also were similar to those used in several European population-based studies, conducted by mail and telephone interviews, on the prevalence of chronic pain (Croft et al., 1993; Macfarlane et al., 2001; Smith et al., 2001; Allison et al., 2002; Papageorgiou et al., 2002). Twins were asked about body pain in 3 regions as follows: "In the past 3 months have you had pain in your muscles, bones, or joints lasting at least one week in your: (1) shoulders, arms, or hands? (2) legs or feet? (3) neck, chest, or, back?". CWP was defined as pain experienced in all 3 regions.

2.3. Statistical analysis

Initial descriptive analyses examined the distribution of sociodemographic factors and depression according to IES tercile. The trend across terciles of these variables was statistically tested by using a χ^2 test for trend for proportions or a one-way ANOVA for means. To investigate the association of the IES with CWP, a random-effects model was fitted to the twin data (Goldstein, 1995). This approach is appropriate because observations within twin pairs cannot be assumed to be statistically independent, an assumption which classical statistical approaches make for estimation and testing. This type of data is considered to be multilevel or clustered, where twins are the cluster. The random-effects model accounts for the lack of independence by using a random-effects term to model the between-pair variance. Additionally, these models can be used with incomplete data, so that half-pairs (in which data on CWP are available from only one member of a pair) can still contribute to portions of the estimation and testing.

We initially modeled the association between the IES and CWP to estimate the overall effect in all twin pairs. In the analysis, we created indicator variables for each tercile of the IES, with the lowest tercile serving as the reference level, to obtain odds ratios and 95% confidence intervals. To statistically test for trend, we conducted an analysis using the continuous IES scores. This overall model specification represents a weighted average of within- and between-pair information (Begg and Parides, 2003). We then obtained separate estimates of the IES-CWP association within and between pairs. In this context, the between-pair effects are an estimate of the IES-CWP association unadjusted for familial environment and genetic influence, whereas the within-pair effects are adjusted for shared familial influences in DZ twins and both shared familial and genetic influences in MZ twins. If adjusting for factors that twins share (i.e., shared familial environment and genetics) eliminates the association between IES and CWP as seen in the within-pair effect, then it is possible to conclude that these shared factors contribute to the IES-CWP association. Alternately, if the adjusted association (within-pair effect) is attenuated but still significant, it suggests that the IES-CWP association in part is explained by shared familial factors in DZ twins and familial and genetics factors in MZ twins. Lastly, if within-pair and between-pair effects are similar, it suggests that familial and genetic factors may not play a significant role in the association between IES and CWP.

In our subsequent modeling, we specified within and between effects separately for MZ and DZ pairs. The DZ within-pair odds ratios are adjusted for familial as well as some genetic influences; DZ twins share a similar family environment, but they share only 50% of their genes on average. Because MZ twins share identical genes, the within-pair effect is an estimate adjusted for both familial and genetic factors. Thus, significantly greater within-pair effects for DZ than MZ twins would suggest shared genetic influence on both CWP and IES. The resulting odds ratios were adjusted for age, sex, race, marital status, education, body mass index, and depression. We used SAS software, Version 8.2 for all statistical analyses (SAS Institute, 2000).

Table 1
Socio demographic and clinical characteristics of all twins and across terciles of the Impact of Events Scale

Variable	Total ($n = 3,740$)	Impact of Events Scale scores		
		Tercile 1[a] ($n = 1,154$)	Tercile 2 ($n = 1,186$)	Tercile 3 ($n = 1,153$)
Monozygotic (%)	56	55	57	57
Age, *mean* (*SD*)	33.0 (14.8)	34.3 (15.7)	32.5 (15.0)	32.1 (13.7)
Females[b] (%)	61	51	61	71
White (%)	87	87	88	86
Married[b] (%)	33	37	32	28
Education				
Less than college (%)	43	43	42	45
College (%)	46	45	47	47
Graduate school[b] (%)	11	13	12	8
Body mass index, *mean* (*SD*)	24.7 (5.0)	24.9 (5.0)	24.5 (5.0)	24.7 (5.2)
CWP[b] (%)	7	4	8	10
PTSD[b] (%)	3.8	1.3	2.3	8.4
Depression[b] (%)	20	9	18	34

[a] Impact of Events Scale score tercile ranges: tercile 1 = 0–6; tercile 2 = 7–24; tercile 3 = 25+.
[b] $P_{trend} < 0.01$.

3. Results

Table 1 describes the socio demographic and clinical characteristics of the entire sample and across terciles of IES scores. More than 55% of the sample consisted of MZ twins, the mean age was 33 years, 61% of the twins were female, and 62% had some college education. The prevalence of self-reported depression was 20%. We observed an increasing trend of CWP, self-reported PTSD and depression, and female gender with higher IES scores ($P_{trend} < 0.01$). Conversely being married and having higher graduate-level education was associated with lower IES scores ($P_{trend} < 0.01$).

Table 2 presents unadjusted odds ratios and 95% confidence intervals for the association of the IES with CWP in all twins and separately for MZ and DZ pairs. There was a strong and highly significant association between the IES score and CWP in all twins ($P_{trend} < 0.0001$). Compared to those in the lowest IES tercile, twins in the highest IES tercile were 3.5 times more likely to report CWP. A similar pattern was observed in both MZ and DZ twin pairs.

Table 3 displays the between- and within-pair associations of the IES and CWP separately in MZ and DZ pairs, adjusted for age, sex, race, marital status, education, body mass index, and depression. The between-pair effects in MZ and DZ twins showed a strong association of IES with CWP ($P_{trend} = 0.01$ in MZ pairs; $P_{trend} = 0.01$ in DZ pairs), but did not differ according to zygosity ($P = 0.95$). Within-pair trends were significant in both MZ ($P_{trend} = 0.04$) and DZ pairs ($P_{trend} = 0.01$). After adjusting for sociodemographic factors, body mass index, depression, and familial and genetic influences, MZ and DZ twins at the highest IES tercile were 2.6–3.0 times more likely to report CWP than twins in the lowest tercile, suggesting that shared familial and genetic factors may not contribute to the relationship between IES scores and CWP. Although the within-pair effect for DZ twins was slightly larger than that found for MZ twins, the difference was not significant ($P = 0.52$).

4. Discussion

We found that symptoms of PTSD, as measured by the IES, were strongly related to the presence of CWP. Further, the increased prevalence of CWP across terciles of increasing IES scores was strong and significant even

Table 2
The association of the Impact of Events Scale and chronic widespread pain in monzygotic and dizygotic twins

Impact of Events Scale	All twins		Monozygotic twins		Dizygotic twins	
	Odds ratio	95% CI[a]	Odds ratio	95% CI	Odds ratio	95% CI
Tercile 1[b]	1.0	–	1.0	–	1.0	–
Tercile 2	2.4	1.6–3.7	2.3	1.3–4.1	2.6	1.4–4.9
Tercile 3	3.5	2.3–5.3	3.8	2.2–6.6	3.1	1.7–5.9
	$P_{trend} < 0.0001$		$P_{trend} < 0.0001$		$P_{trend} < 0.0001$	

[a] CI = confidence interval.
[b] Impact of Events Scale score tercile ranges: tercile 1 = 0–6; tercile 2 = 7–24; tercile 3 = 25+.

Table 3
Between- and within-pair association of the Impact of Events Scale and chronic widespread pain in monozygotic and dizygotic twins adjusted for sociodemographic factors, body mass index, and depression

Zygosity		Overall		Between pairs[c]		Within pairs[d]	
		Odds ratio[a]	95% CI[b]	Odds ratio[a]	95% CI	Odds ratio[a]	95% CI
Monozygotic	Tercile 1[e]	1.0	–	1.0	–	1.0	–
	Tercile 2	2.2	1.2–4.1	2.9	1.3–6.7	1.6	0.7–3.9
	Tercile 3	2.7	1.4–4.9	2.8	1.3–6.0	2.6	1.0–6.6
		$P_{trend} < 0.0001$		$P_{trend} = 0.01$		$P_{trend} = 0.04$	
				P between vs. within $= 0.55$			
Dizygotic	Tercile 1	1.0	–	1.0	–	1.0	–
	Tercile 2	3.1	1.5–6.5	2.9	1.2–7.1	3.5	1.2–9.8
	Tercile 3	3.2	1.5–6.6	3.3	1.4–8.1	3.0	1.0–8.6
		$P_{trend} < 0.001$		$P_{trend} = 0.01$		$P_{trend} = 0.01$	
				P between vs. within $= 0.58$			

[a] Odds ratios are adjusted for age, sex, race, marital status, education, body mass index, and depression.
[b] CI = confidence interval.
[c] Interaction test comparing monozygotic vs. dizygotic between-pair effects, $P = 0.95$.
[d] Interaction test comparing monzygotic vs. dizygotic within-pair effects, $P = 0.52$.
[e] Impact of Events Scale score tercile ranges: tercile 1 = 0–6; tercile 2 = 7–24; tercile 3 = 25+.

after adjusting for socio demographic factors, body mass index, and depression. These results are congruent with several other studies. Clinical studies of FM patients have found high rates of PTSD or PTSD symptoms (Benedikt and Kolb, 1986; Sherman et al., 2000; Cohen et al., 2002; Sharp, 2004), and studies conducted in pain clinic patients, female veterans, and a community sample of women have found that individuals diagnosed with FM are at ~3-fold increased risk of experiencing PTSD or PTSD symptoms compared to those without FM (Dobie et al., 2004; Raphael et al., 2004; Roy-Byrne et al., 2004). Taken together, these previous studies have confirmed the association between PTSD and CWP, although none of them adjusted for genetic and shared environmental influences on this relationship.

This is the first study of PTSD symptoms and CWP in a twin population. Several previous studies have demonstrated that both PTSD and CWP in individuals have a familial or genetic component. For example, a family study of Cambodian refugees living in the United States found that parental PTSD was associated with a 5-fold increased risk of PTSD in their offspring (Sack et al., 1995). Findings from a study of male twins from the Vietnam Era Twin Registry suggested that a shared familial vulnerability contributes to the co-occurrence of PTSD and major depression and that genetic factors may mediate this vulnerability (Koenen et al., 2003). Similarly, studies of FM have demonstrated a familial or genetic influence. For example, a high prevalence of FM has been found repeatedly among offspring of mothers with FM, and relatives of people with FM have a lower tender point threshold than the general population (Buskila et al., 1996; Arnold et al., 2004). Another study showed that husbands of women with FM had a high prevalence of FM (Buskila and Neumann, 1997). This is intriguing, because the prevalence of FM in men is substantially lower than in women (Yunus, 2001, 2002) and, more importantly, because familial or environmental influences would be implicated in this association, rather than genetic ones.

Twin studies of other pain conditions also have demonstrated familial and genetic influences. One study of low back and neck pain found that these conditions may be highly heritable, with 52–68% of the variance for low back pain and 35–58% of the variance for neck pain attributable to gene factors (MacGregor et al., 2004). Conversely, a twin study of temporomandibular joint disorder found that environmental factors were the major determinants of variance (Michalowicz et al., 2000). In our study, we examined whether the relationship between PTSD symptoms and CWP was due to familial or genetic factors. The MZ and DZ within-pair effects were similar to the between-pair effects, suggesting that familial factors do not play a role in the relationship between CWP and PTSD symptoms. Likewise, the MZ within-pair effect was only slightly attenuated compared to the DZ within-pair effect. These findings suggest that the strong association between PTSD symptoms and CWP cannot be explained by confounding due to genetic influences. Thus, one can conclude that individual differences in trauma may explain the robust association between PTSD symptoms and CWP. There are, however, other possible factors that vary within a pair, for example medical or social support, which could also confound this relationship.

Although some evidence now exists to support the relationship between PTSD and CWP, the mechanisms remain enigmatic. The relationship between PTSD and CWP has been postulated to be mutually maintaining,

where CWP serves as a traumatic stimulus for the development of PTSD, and the hyper-arousal, stress intolerance, and selective attention typical of PTSD worsen the pain (Sharp and Harvey, 2001). Other researchers have proposed a model of shared vulnerability, in which the relationship of PTSD and pain is mediated by a third factor, such as anxiety sensitivity, which increases vulnerability either to PTSD symptoms or to pain (Asmundson et al., 2002). Still others postulate that baseline abnormalities in hypothalamic pituitary adrenal and autonomic function may serve as a diathesis that predisposes to either CWP or PTSD or both after a traumatic event (McLean et al., 2005). Studies using brain imaging methods, such as functional MRI, to investigate how the brain reacts to psychological trauma and pain have found that pain is processed in more regions than previously thought, and that some of these overlap with regions activated with psychological trauma (Shin et al., 1997; Coghill et al., 1999). Understanding the patterns and linkages of the overlapping brain regions involved in the experience of pain and trauma could shed light on this intriguing association. Regardless of the underlying mechanism, however, our findings strongly support the need to assess for PTSD and CWP comorbidity and to provide adequate treatment for the symptoms of both disorders.

This study has several limitations. First, although the IES has been used extensively as a measure of PTSD symptoms, we were unable to use the complete 15-question version. While the 4 questions eliminated were those least correlated with their respective intrusion or avoidance subscale measures, we are unable to examine the impact of these deletions on the true score. However, the internal consistency of the 11 questions that were retained was quite high. Second, the IES is an indicator of PTSD symptoms that is not anchored to a specific traumatic experience, so the severity or impact of the traumatic experience is unclear. When used in this manner, the IES may in part be measuring a ''trait'' rather than a ''state'' (i.e., a stereotypical response to many traumatic events rather than a specific response to a single event). Finally, our measure of CWP is not ideal because it was designed to screen for FM during a telephone interview. Although 100% sensitive for FM and 100% specific for the absence of pain, the screener has an estimated specificity of 57% and a false positive rate of 43% among individuals with other forms of chronic pain such as rheumatoid arthritis.

In conclusion, our analysis was based on a large, unselected sample of twins identified from the community of licensed drivers in Washington State. Previous studies of PTSD and CWP typically have involved clinical samples with unknown selection biases. We found a strong association between PTSD symptoms and CWP that was not explained by a shared familial or genetic vulnerability to both conditions. Future studies need to examine the viability of mutual maintenance and shared vulnerability models, as well as the central nervous system mechanisms that may play a role in the link between PTSD and pain.

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Therapy Insight: fibromyalgia—a different type of pain needing a different type of treatment

Dina Dadabhoy* and Daniel J Clauw

SUMMARY

In the past decade, we have made tremendous progress in our understanding of fibromyalgia, which is now recognized as one of many 'central' pain syndromes that are common in the general population. Specific genes that might confer an increased risk of developing fibromyalgia syndrome are beginning to be identified and the environment (in this case exposure to stressors) might also have a significant effect on triggering the expression of symptoms. After developing the syndrome, the hallmark aberration noted in individuals with fibromyalgia is augmented central pain processing. Insights from research suggest that fibromyalgia and related syndromes require a multimodal management program that is different from the standard used to treat peripheral pain (i.e. acute or inflammatory pain). Instead of the nonsteroidal anti-inflammatory drugs and opioids commonly used in the treatment of peripheral pain, the recommended drugs for central pain conditions are neuroactive compounds that downregulate sensory processing. The most efficacious compounds that are currently available include the tricyclic drugs and mixed reuptake inhibitors that simultaneously increase serotonin and norepinephrine concentrations in the central nervous system. Other compounds that increase levels of single monoamines (serotonin, norepinephrine or dopamine), and anticonvulsants also show efficacy in this condition. In addition to these pharmacologic therapies, which are useful in improving symptoms, nonpharmacologic therapies such as exercise and cognitive behavioral therapy are useful treatments for restoring function to an individual with fibromyalgia.

KEYWORDS fatigue, fibromyalgia, pain, pathophysiology, treatment

REVIEW CRITERIA

We searched for articles focusing on fibromyalgia in PubMed published between 1988 and 2005. The search terms used were "fibromyalgia", "pathophysiology", and "treatment". All papers identified were English-language, full-text papers. We also searched the reference lists of identified articles for further papers.

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INTRODUCTION

To standardize the definition of fibromyalgia, the American College of Rheumatology (ACR) published criteria for this syndrome in 1990.[1] These criteria require that an individual have both a history of chronic, widespread pain (CWP) and at least 11 of 18 possible tender points. Although the ACR criteria were not intended to be used for diagnosis in clinical practice, the criteria did allow for ongoing, innovative research into the pathophysiology of this condition. It has become clear that fibromyalgia is one of a group of central pain syndromes characterized by aberrant pain processing, possibly against a background of an abnormal or heightened stress response (Figure 1). Moreover, the neurobiological abnormalities interplay with psychosocial and behavioral factors to lead to functional decline. As such, physicians need to understand and intervene at both the biological and behavioral levels of the condition to optimize the treatment and minimize the morbidity of people affected by the syndrome.

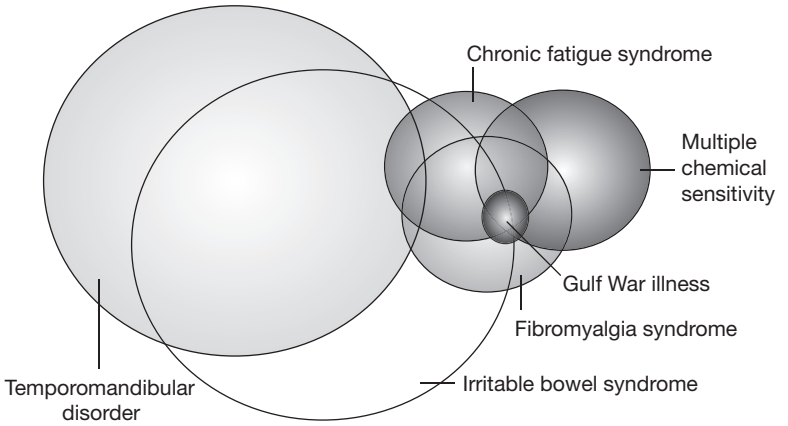
EPIDEMIOLOGY OF CHRONIC, WIDESPREAD PAIN AND FIBROMYALGIA

The prevalence of chronic widespread pain (CWP) in most industrialized countries is 10–11% of the population.[2,3] Although CWP is a part of the research classification of fibromyalgia, as previously noted, the 1990 ACR criteria also requires finding of at least 11 of 18 possible tender points on examination. Using this criteria, the population prevalence of fibromyalgia in industrialized countries has been reported to range from 0.5% to 4%.[4,5]

Since the publication of the criteria, much has been learned about tender points. Research has shown that patients with fibromyalgia have tenderness or decreased pain thresholds, not only at localized areas of tender points, but throughout the entire body.[6,7] It has also been found that, although women are only 1.5 times

more likely than men to experience CWP, they are 11 times more likely to have more than 11 tender points on examination.[2] In addition, population-based studies have shown that tender points are more common in distressed individuals.[8] More sophisticated measures of tenderness have been developed recently that give stimuli in a random, unpredictable fashion. Although these testing paradigms yield results that are not influenced by psychological factors such as distress, individuals with fibromyalgia are still found to be much more tender than healthy controls.[9] Thus, although the number of tender points is associated with distress, tenderness is not. By comparison, CWP, the primary symptom associated with fibromyalgia, is only modestly associated with distress, and distress itself is only weakly associated with the subsequent development of CWP.[10,11] Psychologically 'normal' individuals develop CWP far more than distressed or depressed people, and most individuals with CWP do not have nor subsequently develop distressor depression.

In summary, although many clinicians predominantly associate fibromyalgia with women who display high levels of distress, much of this is an artifact of the ACR criteria requirement of at least 11 tender points. By minimizing these biases through examining CWP in population-based studies, a clearer picture of fibromyalgia can be obtained, and chronic widespread pain becomes much like chronic musculoskeletal pain in any region of the body.



Primary diagnosis	Degree of overlap with secondary condition (%)[67,68]				
	FMS	CFS	IBS	TMD	MCS
FMS	NA	70	32–80	75	55
CFS	35–70	NA	58–92	20	41–67
IBS	32–65[a]	58–92[a]	NA	32-65[a]	ND
TMD	13–18	20	64	NA	ND
MCS	33–55	30	ND	ND	NA

Figure 1 Central pain syndromes that have symptoms overlapping with those of fibromyalgia syndrome. There is overlap of a number of prevalent systemic and regional chronic pain and abnormal sensory conditions that share common mechanisms and effective treatments.[16,65–68] Abbreviations: CFS, chronic fatigue syndrome; FMS, fibromyalgia syndrome; IBS, irritable bowel syndrome; MCS, multiple chemical sensitivity; NA, not applicable; ND, not determined; TMD, temporomandibular disorder. [a]Not numerically represented on diagram.

ETIOLOGY AND PATHOGENESIS

Genetics and environmental influences

Increasing evidence supports a genetic predisposition to fibromyalgia. First-degree relatives of individuals with fibromyalgia display an eightfold greater risk of developing fibromyalgia than those in the general population.[12] Although no confirmed links have been discovered, polymorphisms in the serotonergic 5-hydroxytryptamine (HT) 2A receptor (T/T phenotype), the serotonin transporter, the dopamine 4 receptor and the catecholamine o-methyl transferase enzyme have been seen more frequently in patients with fibromyalgia.[13–15] Notably, these polymorphisms all effect the metabolism or transport of monoamines, compounds that have a critical role in both sensory processing and the human stress response.

In addition to the genetic associations, it is clear that factors external to the individual can enhance expression of symptoms. A number of stressors are temporally associated with the development of either fibromyalgia or chronic fatigue syndrome, including physical trauma (especially involving the axial skeleton and trunk), certain infections (e.g. hepatitis C virus, Epstein–Barr virus, parvovirus, Lyme disease), emotional stress and other regional pain conditions or autoimmune disorders.[16]

Neuroendocrine and autonomic dysregulation

Studies demonstrating alterations of the hypothalamus–pituitary–adrenal axis and the sympathetic nervous system in fibromyalgia and related

conditions support the theoretical link between neural stress systems and symptom expression.[17–21] Overall, the findings indicate a hyperactivity of both the hypothalamus–pituitary–adrenal axis and the sympathetic nervous system in affected individuals; however, there are inconsistencies in the results of these studies. Interestingly, recent work suggests that these abnormalities might represent a 'diathesis' that predisposes individuals to develop the somatic symptoms rather than being directly responsible for the symptoms.[22,23]

Pain processing systems

Once a susceptible individual has symptoms of fibromyalgia, the most consistently detected objective abnormalities involve the pain and sensory processing systems. Numerous experimental pain studies have shown that, although patients with fibromyalgia cannot detect electrical, pressure, or thermal stimuli at lower levels than normal subjects, the threshold at which these stimuli cause pain or unpleasantness is lower for fibromyalgia patients.[24,25] The aberrant pain perception is probably the result of several factors, but one key aspect is central pain (enhanced nociceptive sensation caused by proximal neural activities in the absence of peripheral input). This assertion is further supported by the lack of consistent peripheral abnormalities in patients with fibromyalgia. Nonetheless, the role peripheral input has in the production or amplification of central pain remains unclear and continues to be explored.[26]

Investigators are examining the pain processing pathways to understand the neuropathology involved in augmented, central pain. Just as the immune system involves proinflammatory and anti-inflammatory cytokines, pain processing systems involve compounds that are generally pronociceptive (i.e. increase the sensitivity of pain processing systems) or antinociceptive. Biochemical studies performed on samples from patients with fibromyalgia have supported the notion that the pathology might be due to high levels of pronociceptive compounds or low levels of antinociceptive compounds, or both. Four studies have identified a much higher level of the pronociceptive substance P in the cerebrospinal fluid (CSF) of patients with fibromyalgia than in the CSF of control subjects.[27] An elevated level of substance P is not specific for fibromyalgia, because it occurs in other chronic pain states, such as chronic, daily headaches and the chronic neck or shoulder pain associated with whiplash injury.[28,29] Thus, a high level of substance P seems to be a biological marker of the presence of chronic pain.

In proximal pronociceptive transmission, the ascending pathways travel from the spinal cord to the brainstem and several distinct areas of the thalamus, which relays information to cortical regions that mediate different aspects of pain. These regions include the somatosensory cortex, anterior cingulate cortex, and insular cortex. Animal studies have also focused on the spinoparabrachial pathways leading to the amygdala, hypothalamus and other limbic structures, which might play roles in emotional reactions to pain (e.g. fear, aversion) and in regulating descending control systems.[30] Although hyperactivity of pronociceptive pathways might have a role in fibromyalgia, there are more data suggesting that fibromyalgia could be related to a decrease in the activity of descending, antinociceptive pathways.[31,32] Beginning in the limbic forebrain structures (anterior cingulate cortex, frontal cortices, and amygdala) or subcortical structures (midbrain periaqueductal grey and locus ceruleus) and passing to the spinal cord, either directly, or indirectly through the rostral ventromedial medulla, these antinociceptive pathways are continually active and, under normal conditions, inhibit the upward transmission of pain.

The two principal descending antinociceptive pathways in humans are the opioidergic and mixed serotonergic–noradrenergic pathways. Current evidence suggests that the opioidergic systems might be maximally activated in individuals with fibromyalgia, as evidenced by high enkephalin levels noted in the CSF of fibromyalgia patients.[33] The decrease in descending antinociceptive activity, therefore, is likely to occur because of deficiencies in the other antinociceptive pathway, the serotonergic–noradrenergic pathway. Studies have shown that the principal metabolite of norepinephrine, 3-methoxy-4-hydroxyphenethylene, is at a low level in the CSF of patients with fibromyalgia.[34] Similarly, there are data suggesting that patients with fibromyalgia have low levels of serotonin and its precursor, L-tryptophan in their serum, as well as reduced levels of the principal serotonin metabolite, 5-hydroxyindole acetic

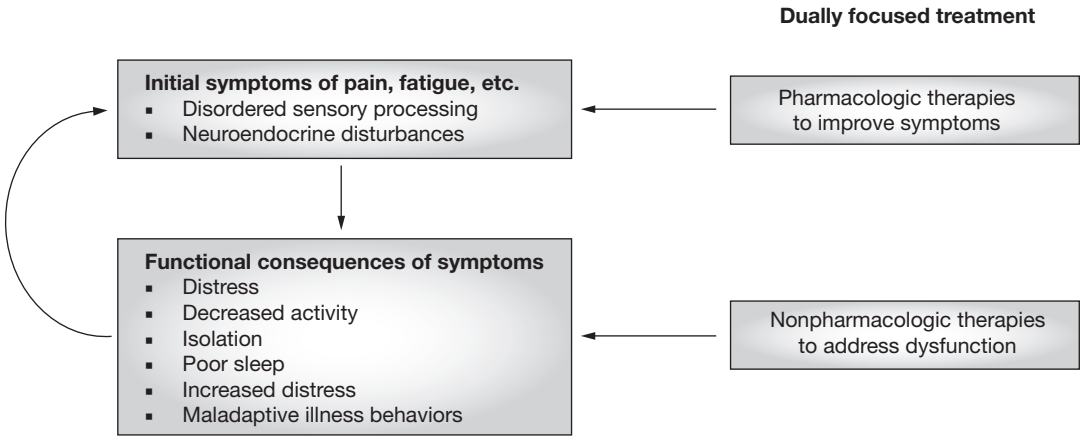


Figure 2 Treatments to break the cycle of worsening symptoms of fibromyalgia. Fibromyalgia symptoms can lead to maladaptive behaviors and decreased function, which can further worsen patients' symptoms. To break this cycle, a dually focused treatment that includes both pharmacologic and nonpharmacologic therapies is recommended.

acid, in their CSF.[34,35] Conversely, a descending serotonergic pathway from the rostral ventromedial medulla to the spinal cord that might facilitate pain modulation through the use of 5HT3 receptors has been noted in animal studies.[30] The antinoceptive effect of blocking these spinal 5HT3 receptors with selective antagonists suggests these receptors have a pronociceptive role.

Treatment studies have lent support to the notion that reductions in norepinephrine-mediated and serotonin-mediated descending antinociceptive pathways are at least partly responsible for the allodynia and hyperalgesia apparent in subsets of fibromyalgia. Nearly any type of compound that simultaneously raises both serotonin and norepinephrine has been shown to be efficacious in this and other central pain conditions, as is discussed later. By contrast, long-term administration of opioids to patients with fibromyalgia seems to have limited efficacy, although this has not been tested formally in a randomized, controlled trial (RCT).

Behavioral and psychological factors

In addition to neurobiological mechanisms, behavioral and psychological factors have an important role in symptom expression and, more notably, in the functional decline of many patients with fibromyalgia (Figure 2). As previously noted, population-based studies have demonstrated that distress can lead to pain, and pain to distress. In the latter instance, pain and other symptoms of fibromyalgia might cause individuals to function less well in the various aspects of their lives. They might have difficulties with family members and co-workers, which can exacerbate symptoms and lead to maladaptive illness behaviors such as cessation of pleasurable activities and reductions in activity and exercise. In the worst cases, patients become involved in the disability and compensation systems, a decision that almost ensures their condition will not improve.[36] The psychosocial factors that influence the experience of pain are not, however, unique to fibromyalgia, but have a prominent role in symptom expression in all rheumatic diseases. In fact, in conditions such as rheumatoid arthritis and osteoarthritis, nonbiological factors such as level of formal education, coping strategies and socioeconomic variables account for more of the variation in pain and disability than biological factors such as joint-space width or sedimentation rate.[37,38]

Given the biopsychosocial nature of fibromyalgia, several groups have attempted to identify subsets of individuals with this condition that might present differently or respond differentially to treatment.[39,40] One group examined how assorted degrees of depression, types of maladaptive cognitions and levels of hyperalgesia might interact to lead to different subsets of patients. The three subsets identified

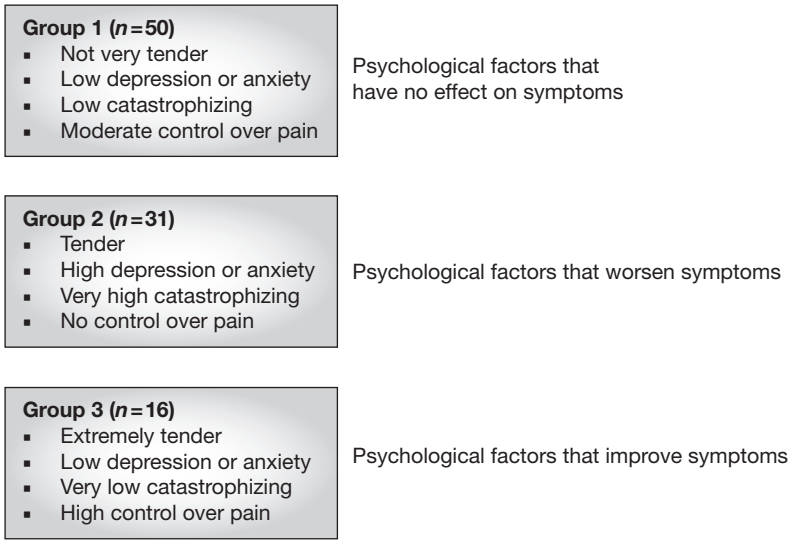


Figure 3 Subsets of fibromyalgia patients. Three groups of fibromyalgia patients with varying levels of tenderness, comorbid psychiatric conditions, and cognitions regarding pain (catastrophizing) have been identified.[40]

are noted in Figure 3. The characterizations of the subgroups suggest a key point: in some resilient individuals, positive psychological and cognitive factors might actually 'buffer' neurobiological factors that lead to pain and distress, possibly by affecting the supraspinal pain modulatory pathways.

Functional-imaging studies have been instructive with regard to how these comorbid mood disorders or cognitions might influence pain processing in fibromyalgia. In one such study, functional MRI was performed in 30 fibromyalgia patients with variable levels of depression, before and after experimental pain testing, to determine how the presence or absence of depression influenced the pain report.[41] Neither the level of depressive symptomatology nor the presence of absence of major depression influenced the degree of neuronal activity in brain regions responsible for coding for the sensory intensity of pain (e.g. the primary and secondary somatosensory cortices). As expected, the depressed individuals displayed greater activity in brain regions known to be responsible for the affective and cognitive processing of pain, such as the amygdala and insula. Another study, with similar methodology, examined how the presence of absence of catastrophizing (having a very negative or pessimistic view of their pain) might influence a patient's pain report in fibromyalgia.[42] In contrast to depression, which did not seem to influence the sensory processing of pain, catastrophizing was associated with increased neuronal activity in the sensory coding regions. Studies that examined the perceptual differences among patient groups, using paradigms that do not involve the administration of noxious stimuli, have not shown a relationship between catastrophizing and perception.[43] The influence of catastrophizing on pain perception, therefore, might be modulated by the perceived threat value of the stimulus.

These studies provide empirical evidence of how pain-related cognitions like catastrophizing can, independently of self-reported depression, affect the experience of pain; moreover, these studies demonstrate the value of positive coping responses. Cognitive behavioral therapy, which aims to identify and modify maladaptive beliefs and increase the use of adaptive cognitive and behavioral coping skills, has been shown to be efficacious in improving the physical and psychological functioning of patients with fibromyalgia.[44]

THERAPY

Progress in the understanding of fibromyalgia has led to improved therapeutic options for patients with this condition. Clinic-based evidence supports a multifaceted program emphasizing education, certain medications, exercise, and cognitive therapy.[44]

Diagnosis and education

Once a physician rules out other potential disorders, an important and at times controversial step in the management of fibromyalgia is making the diagnosis. Despite some assumptions that being 'labeled' as having fibromyalgia might adversely affect patients, in a study by White *et al.*, patients showed significant improvements in health satisfaction and symptoms after being diagnosed with fibromyalgia.[45] Nonetheless, in certain individuals, for example adolescents or individuals who might use the label as an excuse for maladaptive illness behavior, the preferred route might be not to label. Regardless of whether or not the label is used, the diagnosis of fibromyalgia should be coupled with patient education, which has been shown in many RCTS to be effective.[44]

Pharmacologic therapies

The most frequently studied pharmacologic therapy for fibromyalgia comprises low doses of tricyclic compounds. Most tricyclic antidepressants (TCAs) increase the concentrations of serotonin or norepinephrine, or both, by directly blocking their respective reuptake. Despite tolerability problems, the use of TCAs (particularly amitriptyline and the biologically similar cyclobenzaprine) to treat the symptoms of pain, poor sleep and fatigue associated with fibromyalgia is supported by several RCTs.[46] The tolerability of TCAs can be improved by beginning with a low dose (e.g. 5–10 mg), giving the dose a few hours before bedtime, and slowly escalating the dose.

Because of a better side-effect profile, newer antidepressants, including selective serotonin reuptake inhibitors (SSRIs), are frequently used in fibromyalgia. The SSRIs fluoxetine, citalopram and paroxetine have each been evaluated in randomized, placebo-controlled trials in fibromyalgia.[44,47–49] In general, the results for SSRIs in fibromyalgia have been similar to the results for other pain conditions. The newer, more potent SSRIs (e.g. citalopram) seem to be less efficacious than the older SSRIs, perhaps because the latter have noradrenergic activity at higher doses.[50]

Since TCAs (and SSRIs, such as fluoxetine and sertraline, at high doses) that have the most balanced reuptake inhibition are the most effective analgesics, many in the pain field have concluded that dual-receptor inhibitors, including serotonin–norepinephrine reuptake inhibitors (SNRIs) and norepinephrine–serotonin reuptake inhibitors, might be of more benefit than purely serotonergic drugs.[50] These drugs are pharmacologically similar to some TCAs in their ability to inhibit the reuptake of both serotonin and norepinephrine, but differ from TCAs in being generally devoid of significant activity in other receptor systems. This selectivity results in diminished side effects and enhanced tolerability. Available data for the first SNRI, venlafaxine, support its use in the management of neuropathic pain, and retrospective trial data demonstrated that this compound is also effective in the prophylaxis of migraine and tension headaches.[51] Two studies in fibromyalgia have yielded conflicting results, with only the study that used a higher dose of venlafaxine showing efficacy.[44] Two new SNRIs, milnacipran and duloxetine, have also been studied in multicenter trials.[52,53] In a phase II trial evaluating milnacipran, statistically significant differences were noted in overall improvement, physical functioning, level of fatigue and degree of reported physical impairment. In a trial of duloxetine, treated patients had decreased self-reported pain and stiffness and a reduced number of tender points compared with patients given placebo. In the two above studies, as well as most studies that have used antidepressants as analgesics, the beneficial effects on pain and other symptoms were independent of the drug effect on mood, thus suggesting that the analgesic and other positive effects of this class of drugs in fibromyalgia are not simply due to their antidepressant effects. A selective 5HT3 antagonist has also been shown to be effective in a European RCT.[54]

Antiepileptic drugs are widely used in the treatment of various chronic pain conditions, including postherpetic neuralgia and painful diabetic neuropathy.[55] Pregabalin is a gamma-aminobutyric acid analog, which is approved for the treatment of neuropathic pain. A recent double-blinded, randomized, placebo-controlled trial demonstrated the efficacy of pregabalin in the treatment of pain, sleep disturbances and fatigue in fibromyalgia.[56] Gabapentin, a compound with similar pharmacology to pregabalin, is specifically indicated for the treatment of postherpetic neuralgia, and studies support its use in the symptomatic treatment of a variety of pain states as well as headache prophylaxis.[55,57] Another antiepileptic compound, clonazepam, has demonstrated efficacy in treating temporomandibular disorder and associated jaw pain, and is also useful in the treatment of restless legs syndrome.[55]

Sedative–hypnotic compounds are widely used by fibromyalgia patients. Studies on the use of certain nonbenzodiazepine hypnotics in fibromyalgia, such as zopiclone and zolpidem, have been published; their results suggest that these agents can improve the sleep patterns and, perhaps, fatigue of fibromyalgia patients, although they had no significant effects upon pain. In contrast, gamma-hydroxybutyrate (also known as sodium oxybate), a precursor of gamma-aminobutyric acid with powerful sedative properties, was recently shown to improve fatigue, pain and sleep architecture in patients with fibromyalgia.[58] Note, however, that this agent is a scheduled substance, because of its potential for abuse.

Pramipexole is a dopamine agonist indicated for Parkinson's disease that has shown utility in the treatment of periodic leg movement disorder.[59] Recent studies suggest that this compound might improve both pain and sleep in patients with fibromyalgia.[60] Tizanidine is a centrally acting alpha-2 adrenergic agonist approved by the FDA for the treatment of muscle spasticity associated with multiple sclerosis and stroke. The literature suggests that this agent is a useful adjunct for treating several chronic pain conditions, including chronic, daily headaches and lower-back pain. A recent trial reported significant improvements in several parameters in patients with fibromyalgia, including sleep, pain and quality of life.[61] Of particular interest was the demonstration that treatment with tizanidine resulted in a reduction in substance P levels in the CSF of patients with fibromyalgia.

There have been no adequate RCTs of opiates in fibromyalgia, and many in the field (including the authors) have not found this class of compounds to be effective in clinical experience. Tramadol is a compound that has some opioid activity (weak mu-agonist activity) combined with serotonin–norepinephrine reuptake inhibition. This compound does seem to be somewhat efficacious in the management of fibromyalgia, both as an isolated compound and as fixed-dose combination with the nonopiate analgesic acetaminophen.[59]

Nonsteroidal anti-inflammatory drugs and acetaminophen are used by a large number of fibromyalgia patients. Although numerous studies have failed to confirm their effectiveness as analgesics in fibromyalgia, there is limited evidence that patients might experience enhanced analgesia when treated with combinations of nonsteroidal anti-inflammatory drugs and other agents. This phenomenon might be the result of concurrent peripheral pain conditions (i.e. osteoarthritis or tendonitis) present in some individuals; alternatively, comorbid peripheral pain generators might lead to central sensitization and worsening of central pain.

Nonpharmacologic therapies

The two best-studied nonpharmacologic therapies are cognitive behavioral therapy and exercise. Both of these therapies have been shown to be efficacious in the treatment of fibromyalgia (as well as a plethora of other medical conditions), and can lead to sustained (e.g. longer than 1 year) improvements, especially when an individual complies with therapy.[44,62] Alternative therapies have been explored by patients managing their own illness and by health-care providers. As with other diseases, there are few controlled trials to advocate their general use. Trigger-point injections, chiropractic manipulation, acupuncture and myofascial release therapy are among the more commonly used modalities, which achieve varying levels of success. Two recent randomized, sham-controlled trials of acupuncture in fibromyalgia showed no difference in efficacy between the active-treatment and sham-treatment groups.[63,64] There is some evidence that the use of alternative therapies give patients a greater sense of control over their illness. In instances where this sense of control is accompanied by an improved clinical state, the decision to use these therapies is between physicians and patients themselves.

CONCLUSION

Chronic pain and fatigue syndromes such as fibromyalgia represent a part of a clinical spectrum of overlapping disorders that afflict a significant portion of the general proportion. Data suggest that there is a familial tendency to develop these disorders, and that exposure to physical, emotional, or environmental stressors might trigger the initiation of symptoms. Once the illness develops, the majority of the symptoms are probably mediated by central-nervous-system mechanisms. Management strategies for fibromyalgia are similar to those for other chronic illnesses, where empathetic health-care providers are encouraged to develop a partnership with their patients. At one end of the continuum, there is the individual with fibromyalgia that responds to a single medication, or a graded, low-impact exercise program. At the other end of the continuum is the tertiary-care patient with high levels of distress, who has no sense of control over their illness, little social support, and has looked to the disability and compensation systems to try to solve their problem. For this individual, and many others in between the two poles, multimodal programs that integrate nonpharmacologic (especially exercise and cognitive behavioral therapy) and pharmacologic therapies are required.

KEY POINTS

- Fibromyalgia syndrome overlaps with a number of systemic and regional chronic pain and abnormal sensory conditions that share mechanisms and effective treatments
- Population-based studies suggest that chronic widespread pain (fibromyalgia without the misconceived clinical reliance on tender points) is only slightly more common in women than men, and only modestly associated with distress
- Aberrant pain and sensory processing caused by spinal and supraspinal alterations is the most consistently detected abnormality in fibromyalgia syndrome
- Neuroactive compounds, especially those that raise central levels of norepinephrine and serotonin, are effective in improving the symptoms of fibromyalgia syndrome and should be first-line therapy
- Exercise and cognitive behavioral therapy are effective and essential in the treatment of fibromyalgia syndrome

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The association between experimental and clinical pain measures among persons with fibromyalgia and chronic fatigue syndrome

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Abstract

Evoked or experimental pain is often used as a model for the study of clinical pain, yet there are little data regarding the relationship between the two. In addition, there are few data regarding the types of stimuli and stimulus intensities that are most closely related to clinical pain.

In this study, 36 subjects with fibromyalgia (FM), chronic fatigue syndrome (CFS), or both syndromes were administered measures of clinical pain and underwent a dolorimetry evaluation. Subjects also underwent experimental pain testing utilizing heat and pressure stimulation. Stimulation levels evoking low, moderate and high sensory intensity, and comparable levels of unpleasantness, were determined for both types of stimuli using random staircase methods. Clinical pain was assessed using visual analogue ratings and the short form of the McGill Pain Questionnaire (MPQ).

Ratings of heat pain sensation were not significantly associated with clinical pain ratings, with the exception of unpleasantness ratings at high stimulus intensities. Pain threshold and tolerance as assessed by dolorimetry were significantly associated with average measures of clinical pain. Both intensity and unpleasantness ratings of pressure delivered using random staircase methods were significantly associated with clinical pain at low, moderate and high levels, and the strength of the association was greater at increasingly noxious stimulus intensities.

These findings suggest that random pressure stimulation as an experimental pain model in these populations more closely reflects the clinical pain for these conditions. These findings merit consideration when designing experimental studies of clinical pain associated with FM and CFS.

Keywords: Fibromyalgia; Chronic fatigue syndrome; Chronic pain; Experimental pain

1. Introduction

Experimental studies designed to deliver noxious stimuli to subjects under controlled conditions are frequently used to make inferences about clinical pain conditions. Despite this, little is known about the

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relationship between experimental pain perception and clinical pain, and there is a lack of research on the experimental methods and types of stimuli that are most highly associated with clinical pain (Gracely, 1999). Such studies are highly important as evoked pain is increasingly being used to study central nervous system (CNS) abnormalities associated with clinical pain conditions such as fibromyalgia (FM), temporomandibular disorders, vulvodynia, and other entities (Geisser et al., 2003; Giesecke et al., 2004; Diatchenko et al., 2005; Petzke et al., 2003a). While pain is not a central feature of chronic fatigue syndrome (CFS), five of eight minor criteria (of which four are necessary to make the diagnosis) for CFS are pain-based (Fukuda et al., 1994). Common CNS abnormalities have been proposed to underlie all of these disorders (Clauw and Chrousos, 1997), and determining the experimental methods that best reproduce the clinical abnormalities associated with these conditions is crucial to their study.

Previous research has shown that persons with FM display heightened responsiveness to auditory tones (McDermid et al., 1996), contact thermal heat in both the noxious and innocuous ranges (Geisser et al., 2003; Kosek et al., 1996; Kosek and Hansson, 1997; Lautenbacher et al., 1994; Staud et al., 2001), ischemic pain (Kosek and Hansson, 1997), pressure applied to the thumb (Gracely et al., 2002; Petzke et al., 2003a) and electrical stimulation (Lautenbacher et al., 1994). Differences between FM subjects and controls have also been observed using methodologies that stimulate abnormal temporal summation of pain or wind-up (Staud et al., 2001, 2003) and the regulation of diffuse noxious inhibitory controls (Kosek and Hansson, 1997). However, only a few studies have examined how these abnormalities relate to the experience of clinical pain. Lautenbacher et al. (1994) reported low associations between measures of clinical pain and responses to electrocutaneous stimuli, pressure and heat. The authors also found that pressure pain thresholds at two sites were significantly associated with clinical pain. Staud et al. (2003) found that a combination of variables including measures of wind-up, pain-related negative affect, and tender point counts accounted for 49% of the variance in clinical pain. Further research is needed to determine the types of stimuli and experimental methods that are most highly associated with clinical pain states. In addition, previous research suggests that experimental methods that employ gradually ascending stimulation are more highly associated with psychological factors that may bias pain ratings (Petzke et al., 2003).

In the present study, we examined the relationships between clinical pain and a variety of evoked pain measures including gradually ascending pressure (dolorimetry) and a random staircase method of stimulus presentation of both pressure and heat stimuli. Based on prior research, we hypothesized that the random staircase methods would be more highly associated with measures of clinical pain compared to dolorimetry. In addition, we hypothesized that pressure pain perception would be more highly associated with measures of clinical pain compared to heat pain perception, as previous research has suggested that pressure sensitivity is highly associated with musculoskeletal pain syndromes (Diatchenko et al., 2005; Rollman and Lautenbacher, 2001). Since both momentary and average clinical pain were assessed, we also examined whether evoked pain was more highly associated with patients' usual pain, or more highly correlated with pain at the time of testing.

2. Materials and methods

2.1. Subjects

Thirty-six subjects who met either the 1990 American College of Rheumatology criteria for fibromyalgia (FM) (Wolfe et al., 1990), the diagnostic criteria for chronic fatigue syndrome (CFS) (Fukuda et al., 1994), or both diagnoses, were included in the study. Subjects with CFS had to have at least one pain symptom to be eligible. Eight subjects were diagnosed with FM alone, eight with CFS alone, and 20 fulfilled the diagnostic criteria for both disorders. Twenty-seven were female, and nine were male. Twenty-three were Caucasian, six were African-American, two were Hispanic, two were Asian-American, and three were of other descent. The mean age was 39.6 (SD = 9.2) years. Mean duration of pain was 96.5 months (SD = 80.9). Subjects with psychiatric disorders that did not interfere with study participation were not excluded.

The study was approved by the Georgetown University Medical Center's institutional review board, and informed consent was obtained from all participants for study on the General Clinical Research Center. All patients underwent a comprehensive screening during which the diagnosis was confirmed and co-morbidities were evaluated. Exclusion criteria were severe physical impairment, medical conditions that were capable of causing patients' symptoms (e.g., morbid obesity, autoimmune/inflammatory diseases, cardiopulmonary disorders), uncontrolled endocrine or allergic disorders (i.e., hyper-/hypothyroidism, diabetes, allergic rhinitis), malignancy, severe psychiatric illnesses (e.g., schizophrenia, substance abuse), factors known to affect the hypothalamic pituitary axis (HPA) or autonomic function (e.g., cigarette smoking, daily intake of caffeine exceeding the equivalence of two cups of coffee), or medication usage other than as-needed analgesics (excluding long-term narcotics). We did not exclude subjects with psychiatric conditions that are associated with HPA dysfunction (e.g., major depression). Eleven subjects who fulfilled the diagnostic criteria were excluded as

these subjects did not complete all of the study measures examined in the current manuscript.

Subjects who qualified for inclusion in the study were scheduled for a 2-day study protocol. They were asked to discontinue intake of antidepressants up to four weeks ahead of the appointment (depending on the drug), but were allowed to use non-steroidal anti-inflammatory drugs until three days before the appointment. On the first day of the study, patients completed the self-report questionnaires and were familiarized with the pain testing paradigm. On the following day, they participated in a pain psychophysical testing session.

2.2. Measures

2.2.1. Clinical pain

Clinical pain was assessed using the short-form of the McGill Pain Questionnaire (MPQ; Melzack, 1987). This questionnaire contains 15 pain adjectives, and a total score is obtained by summing responses to all the items. The present pain intensity (PPI) subscale was examined as an indicator of pain intensity at the time of testing. The scale is sensitive to change produced by various pain interventions, and is highly correlated with the parent scale (Melzack, 1987).

Self-report of clinical pain intensity was also obtained by visual analogue scale (VAS) ratings. The scale was 100 mm long and anchored by the statements "no pain" on the left and "the most intense pain imaginable" on the right. Separate VAS scales were used to measure subjects' level of pain on the day of testing and average pain over the past month. VAS ratings have demonstrated good reliability (Boeckstyns and Backer, 1989; Revill et al., 1976) and concurrent validity when compared to other methods of pain measurement (Downie et al., 1978; Jensen et al., 1989).

2.2.2. Pressure and heat pain assessment

Evoked pain was assessed for both pressure and heat stimuli. Pressure pain sensitivity was evaluated by subjective scaling of pain sensations evoked by discrete 5-s pressure stimuli applied to the fixated left thumbnail with a 1-cm^2 hard rubber probe. Previous studies have shown that "neutral" regions, such as the thumb, accurately reflect an individual's overall pressure pain sensitivity (Petzke et al., 2001). The rubber probe was attached to a hydraulic piston, which was connected via a combination of valves to a second piston. Application of calibrated weights to the second piston produced controlled, repeatable pressure pain stimuli of rectangular waveform, that is, subjects experienced no pressure, then the target stimulus pressure when the appropriate weight was placed on the second piston. Subjects rated the intensity and unpleasantness dimensions of pressure pain sensations using a combined numerical (0–20) analog descriptor scale (Gracely et al., 1979). For each dimension, a series of 5-s stimuli were delivered to the right thumbnail in ascending order in 0.5 kg of force per square centimeter (kg/cm^2) increments after an initial stimulus of 0.25 kg/cm^2, up to a maximum of 10 kg/cm^2. A second series of pressure stimuli was administered using the multiple random staircase (MRS) method (Gracely et al., 1988). A software system uses the data collected from the ascending series to compute starting stimulus intensities for another set of stimuli controlled by the method of MRS's. The MRS is an interactive system in which the software logic continuously adjusts the stimulus intensity to maintain ratings at several specific levels. In this implementation, three independent staircases are titrated to produce pain sensations rated between 0 and 1 (no sensation to faint pain), between 9 and 10 (mild–moderate pain), and between 13 and 14 (strong–slightly intense pain) on the 0–20 box scale. In the remainder of this report, these levels are referred to as low, medium, and high. On each trial, the method randomly selects a staircase and delivers the stimulus intensity associated with that staircase. The response determines the next stimulus delivered by that staircase the next time it is selected. This determination is based on the previous response history and uses a dynamically changing step size to estimate the stimulus intensity required to produce the level of pain associated with each particular staircase. The method will deliver 12 stimuli for each of the three staircases, for a total of 36 stimuli delivered over 12 min. If any staircase has not converged after 12 stimuli, the operator will be able to continue the method until convergence is reached or until 72 total stimuli have been delivered.

Heat pain sensations were evoked by a 1 cm diameter contact thermode system. A low-mass electrical heater on a water-perfused cold sink with feedback circuitry delivered precise stimulus waveforms with a ramp rate of 10 °C/s. The thermal stimuli were delivered to the volar surface of the non-IV forearm. As with the pressure testing, both an ascending and a multiple random staircase series of thermal stimuli were presented to each subject. The temperatures required to evoke ratings of low, medium, and high pain intensity and unpleasantness were calculated for each subject.

2.2.3. Dolorimetry

A dolorimeter with a 1 cm^2 tip was used to determine pain threshold and tolerance levels bilaterally at the thumb and lateral epicondyle. Pressure was increased at a rate of 1 kg/cm^2 per second and subjects were instructed to indicate when they first perceived pain (threshold) and when the pain became unbearable (tolerance). Pressure was stopped once the pain became unbearable or if 12 kg/cm^2 of pressure was reached. These sites were chosen as previous research has shown that these points are highly correlated with overall tenderness (Petzke et al., 2001). The measures from each

side of the body were averaged to produce one value for each stimulus site.

3. Results

Table 1 shows the means and standard deviations for pressure and thermal intensities needed to evoke sensations of mild, medium, and high sensory intensity and unpleasantness using the random staircase procedure, and displays the threshold and tolerance averages for dolorimetry measured at the thumb and lateral epicondyle.

An initial analysis examined whether the patient groups differed on any of the clinical or experimental pain measures. Oneway analysis of variance (ANOVA) revealed that the groups significantly differed on VAS ratings of pain today ($F = 7.0$, $p = .003$) and pain over the past month ($F = 4.1$, $p = .03$). Post hoc tests (Duncan) indicated that subjects diagnosed with both FM and CFS had higher ratings of pain today compared to the other two groups, and had higher VAS ratings of pain over the past month compared to subjects diagnosed with CFS alone. In addition, the groups significantly differed on pain threshold ($F = 3.2$, $p = .05$) and tolerance ($F = 3.2$, $p = .05$) assessed by dolorimetry at the lateral epicondyle. Post hoc tests revealed that subjects with CFS alone had significantly higher pain threshold and tolerances compared to subjects with both CFS and FM.

Correlations between the clinical pain measures, dolorimetry, and heat and pressure pain measures (stimulus intensities needed to evoke different levels of pain sensation) are presented in Table 2. The correlations indicate that pressure stimuli delivered using the random staircase method were significantly associated with ratings on the MPQ for both unpleasantness and intensity at all stimulus levels, with the exception of low unpleasantness ratings. In addition, pressure stimuli at high levels of intensity and unpleasantness were significantly associated with VAS ratings of pain over the past month. The magnitude of this association became greater as the stimulus intensity increased. Measures of pain threshold and tolerance assessed by dolorimetry at the lateral epicondle were significantly and inversely related to the MPQ total score and average VAS over the past month, indicating lower pain thresholds and tolerance were significantly associated with higher clinical pain. Pain thresholds and tolerances measured at the thumb using dolorimetry were not significantly associated with these same measures. None of the dolorimetry, heat or pressure pain measures were significantly correlated with measures of pain assessed on the day of testing.

Measures of heat pain sensitivity delivered using the random staircase procedure were not significantly associated with clinical pain ratings, with the exception of high unpleasantness ratings and McGill total pain scores and VAS ratings of pain over the past month.

To determine whether the significant correlations obtained between the experimental and clinical pain measures significantly differed across experimental methods, the formula for comparing two correlation coefficients from related samples was utilized (Weinberg and Goldberg, 1979, p. 412). Comparing the associations between intensity and unpleasantness levels and clinical pain assessed by the MPQ utilizing the MRS pressure method versus heat, the associations with

Table 1
Means (SD) of experimental heat and pressure measures

Measure	Mean (SD)
Lateral epicondyle threshold (kg/cm^2)	5.4 (2.5)
Lateral epicondyle tolerance (kg/cm^2)	7.2 (3.0)
Thumb threshold (kg/cm^2)	6.6 (3.0)
Thumb tolerance (kg/cm^2)	8.2 (3.1)
Low pressure intensity (kg/cm^2)	2.3 (1.8)
Medium pressure intensity (kg/cm^2)	4.7 (2.5)
High pressure intensity (kg/cm^2)	6.5 (2.7)
Low pressure unpleasantness (kg/cm^2)	2.7 (2.3)
Medium pressure unpleasantness (kg/cm^2)	5.4 (2.7)
High pressure unpleasantness (kg/cm^2)	7.4 (2.9)
Low heat intensity (°C)	38.3 (2.8)
Medium heat intensity (°C)	43.0 (4.1)
High heat intensity (°C)	46.9 (4.5)
Low heat unpleasantness (°C)	39.3 (3.6)
Medium heat unpleasantness (°C)	44.9 (4.8)
High heat unpleasantness (°C)	48.2 (4.5)

Table 2
Correlations between experimental and clinical pain measures

Measure	McGill total	VAS past month	PPI	VAS today
Dolorimeter				
Lateral epicondyle threshold	−.36*	−.34*	−.17	−.23
Lateral epicondyle tolerance	−.41*	−.35*	−.24	−.30
Thumb threshold	−.22	−.16	−.09	−.11
Thumb tolerance	−.31	−.25	−.20	−.24
Pressure				
Low intensity	−.42*	−.21	−.18	−.23
Medium intensity	−.48*	−.23	−.22	−.24
High intensity	−.52*	−.33*	−.27	−.27
Low unpleasantness	−.30	.00	−.13	−.10
Medium unpleasantness	−.45*	−.19	−.22	−.16
High unpleasantness	−.52*	−.35*	−.27	−.22
Heat				
Low intensity	−.14	−.18	.06	−.11
Medium intensity	−.20	−.31	.02	−.17
High intensity	−.24	−.31	−.03	−.15
Low unpleasantness	−.10	−.07	.03	.00
Medium unpleasantness	−.20	−.24	.01	−.08
High unpleasantness	−.36*	−.35*	−.15	−.17

* $p < .05$.

MRS pressure were significantly higher for the medium ($t = -2.3$, $p = .03$) and high ($t = -2.8$, $p = .01$) intensity stimuli compared to the same levels obtained using MRS heat. A similar result was also obtained for medium ($t = -2.1$, $p = .05$) unpleasantness stimuli. When VAS ratings of pain during the past month were examined, the associations between this measure and stimulation levels obtained using MRS heat and MRS pressure did not differ. The correlations between dolorimetry and clinical pain did not significantly differ from those observed between MRS heat or pressure and clinical pain. The magnitude of the associations between MRS pressure and clinical pain, and dolorimetry and clinical pain, were also not significantly different.

As trends were evident suggesting that higher stimulation levels were more strongly associated with clinical pain compared to less intense levels, these correlations were also compared using the same method noted above. For dolorimetry, associations between dolorimetry and clinical pain comparing the threshold and tolerance measures did not significantly differ. For MRS pressure and heat, the associations across different intensity rating levels also were not significantly different. For unpleasantness ratings, the association between pressure high unpleasantness and VAS ratings of pain over the past month was significantly greater than the association between pressure low unpleasantness and this same measure of clinical pain ($t = -2.8$, $p = .01$). Also, the difference in the associations between pressure low unpleasantness and MPQ scores and high pressure unpleasantness and MPQ scores approached significance ($t - 1.8$, $p = .08$).

4. Discussion

Pain sensitivity determined by pressure stimulation using the multiple random staircase (MRS) procedure was significantly and inversely associated with average measures of clinical pain intensity, while heat was not. Comparing the magnitude of the associations, the correlations between MRS measures of pressure and clinical pain as assessed by the MPQ were significantly higher than those obtained between MRS heat and clinical pain. None of the experimental pain measures were significantly associated with measures of clinical pain assessed at the time of testing. These findings suggest that responses to evoked pressure pain in patients with FM and CFS can be generalized to patients' overall clinical condition, and that fluctuations in clinical pain that may occur during psychophysical testing do not significantly influence evoked pain responses. These findings also suggest that pressure stimulation as an experimental pain model among subjects with FM and CFS more closely reflects the average clinical pain associated with these conditions, and is consistent with other research suggesting that mechanical stimulation is an especially sensitive measure for the analysis of pathology associated with musculoskeletal pain (Diatchenko et al., 2005; Rollman and Lautenbacher, 2001).

In general, ratings given to higher stimulus intensities were more strongly associated with average ratings of clinical pain. These findings highlight the importance of evoked pain studies and provide further justification for the use of suprathreshold stimuli in experimental pain paradigms. The findings also suggest that experimental application of innocuous stimuli as a model for clinical pain may not be as generalizable to clinical pain conditions. In addition, the findings suggest that methods used to assess pain thresholds may not be as generalizable to clinical pain compared to studies employing suprathreshold methods of pain stimulation. This conclusion needs to be interpreted cautiously as significantly higher correlations between higher levels of experimental pain stimulation and clinical pain were only obtained for unpleasantness ratings and not intensity ratings, and this finding was only evident using the MRS pressure stimulation method. Further research examining the risk/benefit of noxious stimulus intensities in relation to the generalizability of the findings and subject burden would be beneficial.

Pressure stimulation using both dolorimetry and random staircase methods were both significantly associated with average measures of clinical pain. However, our previous research suggests that random staircase methods are less prone to biases associated with gradually ascending stimuli, and therefore are less likely to be influenced by affective states that frequently accompany pain, such as depression. In the present study, the magnitude of the associations between random staircase measures of pressure sensation and clinical pain as assessed by the McGill were somewhat higher than they were for dolorimetry, although this difference was not statistically significant. Further research is needed to determine the types of evoked pain models that most closely reflect the mechanisms underlying different clinical pain conditions.

It should be noted that the design of the present study is cross-sectional, and therefore no inferences can be made about causality. In addition, this study only examined a few of the experimental pain paradigms published in the literature, and therefore the findings cannot speak to the generalizability of other experimental methods to clinical pain, such as electrical stimulation. Third, the study examined patients with pain associated with FM and CFS, and the findings may not be generalizable to other clinical pain conditions. Fourth, this study examined the correlation between clinical pain intensity and experimental pain perception, and did not examine the ability of experimental methods to discriminate between persons with and without chronic pain. Such a comparison would also be beneficial in examining the validity of various methods of experimental pain.

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Comparison of Clinical and Evoked Pain Measures in Fibromyalgia

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Abstract: **Evoked pain measures such as tender point count and dolorimetry are often used to determine tenderness in studies of fibromyalgia (FM). However, these measures frequently do not improve in clinical trials and are known to be influenced by factors other than pain such as distress and expectancy. The purpose of this investigation was to determine whether evoked pain paradigms that present pressure stimuli in a random fashion (eg, Multiple Random Staircase [MRS]) would track with clinical pain improvement in patients with FM better than traditional measures. Sixty-five subjects enrolled in a randomized clinical trial of acupuncture were observed longitudinally. Clinical pain was measured on a 101-point numerical rating scale (NRS) and the Short Form McGill Pain Questionnaire (SF-MPQ), whereas evoked pressure sensitivity was assessed via manual tender point count, dolorimetry, and MRS methods. Improvements in clinical pain and evoked pain were assessed irrespective of group assignment. Improvement was seen in clinical pain during the course of the trial as measured by both NRS ($P = .032$) and SF-MPQ ($P = .001$). The MRS was the only evoked pain measure to improve correspondingly with treatment (MRS, $P = .001$; tender point count and dolorimeter, $P > .05$). MRS change scores were correlated with changes in NRS pain ratings ($P = .003$); however, this association was not stronger than tender point or dolorimetry correlations with clinical pain improvement ($P > .05$). Pain sensitivity as assessed by random paradigms was associated with improvements in clinical FM pain. Sophisticated pain testing paradigms might be responsive to change in clinical trials.**

Perspective: ***Trials in fibromyalgia often use both clinical and experimental methods of pain assessment; however, these two outcomes are often poorly correlated. We explore the relationship between changes in clinical and experimental pain within FM patients. Pressure pain testing that applies stimuli in a random order is associated with improvements in clinical pain, but this association was not stronger than other experimental techniques.***

Key words: *Pain, fibromyalgia, MRS, tender point, dolorimeter.*

Fibromyalgia (FM), a condition characterized by chronic diffuse pain, is the second most common rheumatologic disorder, affecting 2% to 4% of the population of industrialized countries.[17,31] The 1990 American College of Rheumatology criteria for the diagnosis of FM requires that a patient must report widespread clinical (ie, spontaneous) pain, as well as have 11 of 18 "tender points."[32] Tender points are predefined anatomic points that are present in various areas of the body and are considered to be positive when an individual complains of pain when 4 kg (approximately 9 pounds) of pressure is applied with the examiner's thumb (approximately the amount of pressure required to blanch the examiner's nail).

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Since the American College of Rheumatology criteria for FM were published, there have been considerable data suggesting problems with the validity of the tender point construct, especially when rigidly applied in clinical practice (ie, having less than 11 tender points precludes having FM).[4,30] First, although early studies suggested that FM patients experienced tenderness only in these discrete regions, we now know that individuals with FM display increased sensitivity to pain throughout the body.[15,26] Thus tender points (eg, the mid-trapezius region, epicondyles) appear to represent regions of the body in which everyone is more tender, and individuals who are more diffusely tender will generally have a greater number of tender points. Second, in many clinical treatment trials in FM improvements in clinical pain do not correspond to improvements in tender points.[1,7,8,18,27] For example, in a meta-analysis of the efficacy of antidepressants in FM, Arnold et al[2] found that tender points were among the outcomes least likely to improve with treatment, even if those treatments led to improvements in clinical pain or other relevant parameters such as functional status.

One reason why clinical and experimental pain does not improve in parallel is because they might represent distinct and separate phenomena. However, it is also possible that tender points simply represent an inferior measure of tenderness. From a statistical standpoint this is known to be the case, because tender point counts are not normally distributed within cohorts of FM patients. FM patients are more likely to have 16 or greater tender points than 11 to 15, suggesting inflation in tender point counts. A more fundamental and increasingly recognized problem is that tender points are not a "pure" measure of tenderness and instead are influenced by cognitive and emotional aspects of pain perception. There is a strong correlation between tender point counts and measures of distress in population-based studies.[29] Petzke et al[24] have shown that more sophisticated measures of tenderness that present stimuli in a random or unpredictable pattern are not associated with the measures of distress, suggesting that tenderness per se is not related to distress, but tender points are strongly related to distress.[10] These measures of pain threshold that use randomly presented stimuli have been extensively used in the pain field and have been shown to be correlated with changes in individual pain perception.[5,11,21] However, previous studies with randomly presented stimuli have been largely restricted to cross-sectional trials[23] and have not examined pain longitudinally. This is relevant in light of the importance of studying pain at multiple time points.[19]

The goal of this investigation was to compare randomly presented evoked pressure pain assessments and the more standard methods used in FM (such as the tender point count and dolorimeter), with respect to tracking changes in clinical pain. Participants from a randomized clinical trial of the efficacy of acupuncture in FM served as the cohort for this study, and these individuals had tender point counts, dolorimetry values, and Multiple Random Staircase (MRS) measures performed longitudinally during the course of treatment. A significant correlation between changes in MRS measures and clinical pain would suggest that the previously observed discrepancy between clinical pain and patient tenderness might be due to the methods that have been used to assess tenderness, rather than the fact that tenderness and clinical pain are unrelated constructs.

Methods

Participants

Sixty-five subjects enrolled in a clinical trial of acupuncture in FM[16] who had complete baseline and follow-up data and were included in this analysis. For the purpose of this investigation, data from the 4 different acupuncture treatment arms were combined, resulting in a secondary analysis of this randomized controlled trial.[16] Participants were recruited via announcements in local newspapers and periodicals and screened on the telephone for study eligibility. Potentially eligible subjects were evaluated for inclusion and exclusion criteria in a General Clinic Research Center. To be enrolled in the study, participants were required to (1) have met American College of Rheumatology criteria for the diagnosis of FM for at least 1 year,[32] (2) report widespread pain on more than 50% of days since diagnosis of FM, and (3) be willing to limit the introduction of new medications or treatment modalities for FM symptoms. Subjects were excluded if they (1) had sufficient knowledge of acupuncture techniques to prevent blinded treatment assignment (including previous acupuncture), (2) had a known bleeding diathesis, (3) had an autoimmune or inflammatory disease, (4) regularly used narcotic analgesics daily or had a history of substance abuse, (5) had contraindications to the use of acetaminophen or ibuprofen, which were used as rescue analgesics, (6) were participating in other therapeutic trials, (7) were pregnant or nursing, or (8) were receiving disability payments or were involved in litigation related to FM. Subjects were allowed to continue their normal treatment regime(s) (including the use of antidepressants); however, they were asked not to make any additional changes and not to seek acupuncture treatment outside of the trial.

All eligible subjects were given a full description of the protocol and gave written, informed consent before inclusion. All procedures were approved by the local institutional review board.

Treatment

In this investigation a 2×2 factorial design was used to examine the individual and synergistic effects of both needle location and needle stimulation on the efficacy of acupuncture analgesia.[16] Briefly, subjects were randomly assigned to receive acupuncture needling in (1) traditional locations with stimulation, (2) traditional locations without stimulation, (3) nontraditional locations with stimulation, or (4) nontraditional locations without stimulation. All subjects received treatment in a forced titration paradigm once weekly for 3 weeks, then twice

Week	0	1	2	3	4-5	6	7	8	9-10	11	12	13	14-15
Sessions (per week)	0	1	1	1	0	2	2	2	0	3	3	3	0
Clinical Pain (NRS & SF MPQ)	X			X				X				X	
Evoked Pain (MRS, TP, Dol)	X				X				X				X

Figure 1. Representation of study outcomes and acupuncture sessions by week. TP, tender point; Dol, dolorimeter.

weekly for 3 weeks, and finally 3 times weekly for 3 weeks, with a 2-week washout period between each treatment block (Fig 1). The results of this investigation indicated that 30% to 40% of the participants had a clinically meaningful reduction in pain; however, needle placement and stimulation were not critical. Because the current investigation was interested in the longitudinal relationship between pain and tenderness rather than the specific effect of acupuncture on these domains, data from all 4 treatment groups were combined for these analyses.

Outcomes

Clinical Pain (Numerical Rating Scale and Short Form McGill Pain Questionnaire)

Subjects completed a 101-point numerical rating scale (NRS) and a modified version of the Short Form McGill Pain questionnaire (SF-MPQ) at baseline (week 0) and at follow-up weeks 3, 8, and 13 (Fig 1).[22] The NRS ranged from 0 to 100 points in 5-point increments and was anchored at 0 by "no pain" and 100 by "worst pain imagined". The modified SF-MPQ contained the standard 15 word descriptors with values of 0 (none), 1 (mild), 2 (moderate), and 3 (severe); however, the Present Pain Intensity (PPI) scale was omitted. The SF-MPQ Total score was calculated as the sum of all descriptors, whereas the Affective and Sensory subscores were obtained from the sum of differing subsets of descriptors.[22]

Evoked Pain (Tender Point, Dolorimeter, and MRS)

Subjects received evoked pain testing at baseline and weeks 4, 9, and 15 (Fig 1). During each session all subjects received a tender point exam, followed by the dolorimeter exam and pain assessment by using the MRS.

Tender point. A manual tender point exam was performed as reported previously.[32] Pressure was applied to 18 predetermined locations on each participant's body with the examiner's thumb until 4 kg of pressure was reached. A positive tender point count was scored if the subject reported pain after removal of pressure. The total tender point count was determined as the sum of all positive points.

Dolorimeter. A dolorimeter was used to determine pain threshold and tolerance levels bilaterally at the thumbnail (center of the nail bed) and lateral epicondyle (ie, bony areas). Pressure was increased at a rate of 1 kg/s, and subjects were instructed to indicate when they first perceived pain (threshold) and when the pain became unbearable (tolerance). Pressure was stopped once the pain became unbearable or if 12 kg of pressure was reached.

MRS. Discrete pressure stimuli were applied to the subject's right thumbnail by using a stimulation device that eliminated any direct examiner/subject interaction. The apparatus induced pressure via a hydraulic system connected to a 1-cm^2 hard rubber circular probe that was pressed against the right thumbnail. The thumbnail was chosen because it has been shown to be highly representative for overall pressure sensitivity.[26] The stimulator was positioned over the thumb by a plastic housing, and the hydraulic system was activated by calibrated weights placed on a moveable table. Valves controlled stimulus timing. The combination of valves and calibrated weights allowed controlled and repeatable stimulation.

Pain intensity ratings were recorded on a 21-box numerical descriptor scale.[25] This scale had been constructed from previously quantified verbal descriptors[9,12,13] and has been shown to be sensitive in other studies.[5,14,21,28]

Before the start of the MRS, the equipment was demonstrated and explained by using a scripted text, and a few discrete pressure stimuli were applied to familiarize subjects with the procedure. Additional information and explanations were provided if required. First to determine the subject's pain range, stimuli of 5-second duration were applied to the right thumbnail in ascending order. Initial stimulation pressure was 0.5 kg, and the pressure was increased in 0.5-kg increments up to either a subject's level of pain tolerance or to a maximum of 10 kg.

In the MRS paradigm the stimulus pressure was determined interactively; a computer program continuously adjusted the stimulus pressures in each staircase to produce the same response distribution in each subject.[11] Three staircases were used to titrate stimulus pressures to pain responses of 0.5 (low pain = "faint"), 7.5 (medium pain = "mild"), and 13.5 (high pain = "slightly intense"). The starting points for each staircase were chosen from the discrete ascending series. Each of the 3 staircases delivered 12 stimuli (36 total), and the program switched between staircases in pseudorandomized order. Subjects were instructed that they would receive a series of pressure stimuli within the range of the previous ascending series. Pain intensity ratings were obtained with the respective 21-box numerical descriptor scale de-

scribed above, and interstimulus interval was 30 seconds. The results of the 3 staircases used in this MRS pain assessment method, stimulation pressures (in kg/cm^2) resulting in low, medium, and high pain intensities, were used for further analysis.

Analysis

Data from clinical and evoked pain outcome domains were combined across all 4 treatment groups and analyzed with SPSS software (Chicago, Ill). Data were either hand-entered or scanned via Teleform (Cardiff Software Inc., Bozeman MT), and in either instance the integrity of data entry was double-checked.

Comparisons between dropouts and responders were made by *t* tests for continuous variables and χ^2 tests for categorical variables. Paired *t* tests were performed separately for NRS and SF-MPQ (baseline to week 13) and evoked pain measures (baseline to week 14 or 15) to determine significant overall changes. Percent change scores from baseline were also calculated as an additional measure of sensitivity. To compare evoked and clinical pain measures, bivariate Pearson correlations were made between change scores (baseline −end) in NRS, SF-MPQ, MRS, dolorimeter, and tender point. Pearson correlations between change scores in both clinical and evoked measures were compared by using the following formula[3]:

$$t = (r_{xy} + r_{zy}) \sqrt{\frac{(N-3)(1+r_{xz})}{2(1-r_{xy}^2 - r_{xz}^2 - r_{zy}^2 + 2r_{xy}r_{xz}r_{zy})}} \quad \text{(equation 1)},$$

where r_{xy} is the Pearson correlation coefficient between pain measures x and y, and r_{zy} is the Pearson correlation coefficient between pain measures z and y. The *t* statistic tests the hypothesis that the correlation between change scores in measures x and y is not different from the correlation between change scores in measures z and y. No corrections were made for performing multiple tests. An α-level cutoff of .05 was used to designate statistical significance, whereas an α-level <0.10 was used to denote trends in the data.

Results

Baseline Demographics and Dropout

Of the 114 participants initially randomized to receive treatment, 65 completed the entire study and are included in these analyses. Subject demographics are displayed in Table 1. The majority of subjects were female (92%, 60/65), and the mean age was 48.31 years. There were no differences in age ($P = .317$), race ($P = .903$), gender ($P = .795$), or duration of FM ($P = .821$) between the dropouts and the completers.

Clinical Pain

Participants completed the NRS and the SF-MPQ at baseline and during weeks 3, 8, and 13 (Table 2). Both the NRS and SF-MPQ showed significant changes from baseline to week 13. The NRS was less sensitive to change as compared with the SF-MPQ (NRS: $P = .032$ vs SF-MPQ: $P < .003$). Significant decreases from baseline values were also observed in both the Sensory ($P = .002$) and Affective ($P = .001$) subscores of the SF-MPQ.

Table 1. Demographics

N = 65	*Mean (Standard Deviation)*
Age, y	48.31 (9.50)
Female/total	60/65
Diagnosis years	5.41 (3.87)
Treatments	15.77 (1.63)
Race (white/black/Asian)	59/5/1

Evoked Measures

Participants completed 3 different evoked pain measures (tender point count, dolorimeter, and MRS) during the 2-week assessment periods after each 3-week session of acupuncture. Results of the evoked measures are presented in Table 3. All 3 levels of the MRS (low, medium, and high) displayed significant improvements from baseline to week 14 (all $P < .05$). In contrast, dolorimeter (threshold and tolerance) and tender point counts did not improve significantly. The tender point count was the least sensitive to change, showing a mean 0.21% change from baseline.

Comparison of Evoked and Clinical Pain Measures

To determine the degree of association between evoked and clinical pain improvement, univariate correlations were made for the change scores in these measures for all subjects (Table 4). Analysis of MRS was limited to the medium pressure level (7.5 or mild on the Gracely box scale) because it was more sensitive to change than the low and high levels.

The change scores of MRS and NRS were significantly correlated ($r = -0.387$; $P = .003$), whereas the correlation between the change in tender point and NRS was at the trend level ($r = 0.245$; $P = .064$). Although a larger correlation between change scores in NRS and MRS was observed, the absolute value of this correlation was not significantly greater than the absolute value of the correlation between NRS and tender point ($P > .05$) from equation 1. Dolorimeter change scores were not significantly correlated with changes in NRS (threshold: $r = -0.164$; $P = .221$; tolerance: $r = -0.171$; $P = .199$). The dolorimeter change scores were also not significantly greater than the MRS correlation with NRS ($P > .05$; from equation 1).

The correlation between the change in tender point count and SF-MPQ was significant ($r = 0.273$; $P = .035$), whereas the MRS and SF-MPQ change scores only approached the trend level ($r = -0.211$; $P = .105$). Dolorimeter change scores also displayed a trend toward significant correlations with the SF-MPQ (threshold: $r = -0.245$; $P = .059$; tolerance: $r = -0.224$; $P = .086$). None

Table 2. Change in Clinical Pain Measures

	NRS	McGill (Total)	McGill (Affective)	McGill (Sensory)
Baseline	54.15 (22.99)	13.77 (9.16)	2.95 (2.67)	10.82 (7.08)
Week 3	54.43 (23.40)	11.91 (8.70)	2.44 (2.41)	9.47 (6.75)
Week 8	48.50 (26.92)	10.08 (8.79)	1.75 (2.26)	8.33 (6.94)
Week 13	43.67 (28.24)	9.23 (9.44)	1.71 (2.66)	7.52 (7.13)
% Change base to wk 13	4.31 (75.9)	18.8 (75.0)	44.3 (71.7)	13.9 (78.5)
P (base to wk 13)	0.032*	0.001**	0.001**	0.002**
t (base to wk 13)	2.200	3.470	3.432	3.160
Degrees of Freedom	59	61	61	61

Absolute value of % change (standard deviation) are shown for each measure. All clinical measures showed significant changes with treatment.

*$P \leq .05$.

**$P \leq .01$.

of the correlations between changes in each of the 3 evoked measures and improvement in the SF-MPQ were statistically different (all $P > .05$; from equation 1).

Discussion

Pain measurement in FM has traditionally relied on either self-report of spontaneous clinical pain or the use of evoked pain measures such as the tender point count and dolorimeter. In this investigation we explored the relationship between a number of evoked pain measures and standard clinical pain measures in FM subjects followed over time.

Although both clinical pain measures improved during the course of the study, only one of the evoked pain measures, the MRS, improved after treatment. The dolorimeter displayed weak sensitivity to change during the course of this study, but this was not related to improvements in clinical pain with either the NRS or SF-MPQ. The tender point count displayed a weak correlation with changes in clinical pain (SF-MPQ) and trend toward significance with the NRS, but the tender point measure showed less than a 1% change (1 point) from baseline (Table 3), suggesting that these correlations might be suspect.

In contrast, the MRS not only displayed significant changes from baseline to after treatment, but these changes were correlated with improvements in clinical pain as assessed by the NRS. Although the MRS appeared to track clinical pain (NRS) better than the tender point, this relationship was not statistically significant and therefore represents a trend. These results suggest that previous discrepancies between clinical and experimental pain outcomes used in FM trials[2] could in part be due to methodologic issues.

However, this issue is complicated by the additional finding that MRS change scores were not correlated with improvements in the SF-MPQ. Instead, all experimental measures showed weak associations ($r \sim 0.2$) with SF-MPQ change scores. One possible explanation for this discrepancy is that the 2 clinical pain assessment questionnaires measure differing aspects of clinical pain. In support of this hypothesis our 2 clinical measures displayed different sensitivity to change (SF-MPQ, 18.8% vs the NRS, 4.3%). Replication of these findings requires future trials.

Why Does the MRS Track NRS Changes?

Previous investigations in both psychophysical pain assessment[20] and randomized controlled trials in FM[1,7,8,18,27] have demonstrated weak correlations be-

Table 3. Change in Evoked Pain Measures

		MRS (kg/cm²)			Dolorimeter (kg/cm²)	
	Tender Point Count	Low	Medium	High	Threshold	Tolerance
Base	13.17 (3.63)	0.81 (0.80)	2.58 (1.69)	4.89 (2.43)	3.50 (1.80)	4.92 (2.42)
Weeks 4–5	13.05 (4.54)	1.03 (1.23)	2.81 (1.81)	4.76 (2.30)	3.55 (1.76)	4.89 (2.28)
Weeks 9–10	12.66 (4.30)	1.13 (1.52)	3.04 (1.76)	5.20 (2.52)	3.96 (1.77)	5.44 (2.16)
Weeks 14–15	12.43 (4.58)	1.20 (1.23)	3.41 (1.99)	5.58 (2.54)	3.94 (1.75)	5.25 (2.34)
% Change base to wk 14–15	0.21 (48.7)	112.0 (186.0)	96.1 (237)	32.1 (80.2)	27.1 (60.8)	18.6 (51.6)
P (base to wk 14–15)	0.175	0.006**	0.001**	0.028*	0.075	0.320
t (base to wk 14–15)	1.373	−2.822	−3.550	−2.256	−1.812	−1.003
Degrees of freedom	62	59	62	62	62	62

Absolute value of % change (standard deviation) are shown for each measure. Only MRS (low, medium, and high) showed significant changes with treatment.

*$P \leq .05$.

**$P \leq .01$.

Table 4. Correlation Between Clinical and Evoked Pain Change Scores

	Change NRS		Change McGill Total	
Change Evoked	r	P	r	P
MRS (medium)	−0.387	.003*	−0.211	.105
Tender point	0.245	.064	0.273	.035*
Dolorimeter (threshold)	−0.163	.221	−0.245	.059
Dolorimeter (tolerance)	−0.171	.199	−0.224	.086

Univariate Pearson correlations between change in clinical (baseline − week 13) and change in evoked pain measures (baseline − week 15). Improvement in MRS is significantly correlated with improvement in NRS but not SF-MPQ.
*$P < .05$.

tween clinical and evoked pain measures. Our results replicate these findings but also suggest that this might in part be due to the evoked tenderness measures used.

Within the MRS protocol, pressure stimuli are administered from a remote device that the investigator controls and from which the patients are shielded. Stimuli are presented in a pseudorandom fashion such that the subject cannot anticipate the intensity of the succeeding stimuli, unlike other pain paradigms such as the tender point and the dolorimeter. In the tender point and the dolorimeter the subject has "knowledge" of the stimulus intensities (ie, for a single discrete stimulus, the pressure will be progressively more intense over time), which might result in expectations surrounding the successive stimuli and therefore might introduce bias.[10]

Because pressure stimuli in the MRS are applied from a remote device that the investigator controls and from which the participants are shielded, interpersonal interactions that might influence results are minimized. In addition, discrete pressures are applied in a standardized manner from session to session, in contrast to the tender point count and dolorimetry, in which the rate of rise of examiner pressure (or in the case of the tender point the pressure itself) might vary from one session to the next.

Finally, another potential advantage of the MRS is that this measure has been shown to be less sensitive to psychological factors that might alter pain assessment.[24,29] Both tender point counts and, to a lesser extent, dolorimetry are associated with the affective status of the patient. If an intervention improves pain processing in FM but does not have a primary effect on distress, then it might be expected that the measure not confounded by distress levels might show a trend toward greater change.

Limitations of This Investigation

This investigation has several limitations. First we focused only on FM subjects, and it remains to be seen whether these results can be applicable to other chronic pain states. For example, idiopathic chronic low back pain has similarities to FM in that subjects display increased pain sensitivity as assessed by the MRS.[6] It remains to be seen whether a significant correlation between the MRS and patient's clinical low back pain might exist. Furthermore, the majority of our participants were white women, and as such our results are only applicable to that population.

Second, the intervention in our study was acupuncture. It is not clear whether similar results would be obtained by using either pharmacologic agents or other nonpharmacologic therapies. For example, if this study had examined the use of an antidepressant rather than acupuncture in FM, one might find that the tender point count would perform better than the MRS, because it would detect both changes in pressure pain threshold and changes in distress that an antidepressant might engender. Therapies that result in greater analgesia than acupuncture should be examined for sensitivity of evoked pain measures in FM.

Third, the clinical and evoked pain tests were not performed at precisely the same time. There was at least a 1-week lag from when clinical pain was assessed to when the evoked pain procedures were performed. This lag time could have impacted our relationship between clinical and evoked pain; however, this effect most likely would have biased our results toward the null (ie, the strength of the relationship between clinical and evoked measures most likely decreases, given a greater lag time). More precise timing of evoked and clinical tests might improve the relationship between these measures.

Fourth, there was a high dropout rate in this trial. Although the baseline demographic factors were not different between completers and those who dropped, our results might not be generalized to all patients with FM.

Finally, despite factors in favor of using the MRS for pain measurement, it might not be practical in many settings. The time required to administer the MRS (more than 30 minutes for a single session) is a limiting factor, especially in the clinic, where time is at a premium. The MRS pain assessment methods rely on sensitive equipment to assign the pressures randomly as well as to apply the stimuli, both of which require maintenance and training. These factors might limit the usefulness of this method in the clinical setting. However, in the research setting the MRS procedure is relatively easy to learn and can be performed by trained investigators.

Conclusion

In this investigation we provide evidence that a sophisticated measure of pressure pain threshold such as the MRS might represent an additional tool for tracking changes in FM pain. Future studies should continue to assess evoked pain in a number of ways to determine whether these results can be replicated and generalized to other treatments, as well as other pain syndromes.

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Using fMRI to Dissociate Sensory Encoding from Cognitive Evaluation of Heat Pain Intensity

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Abstract: Neuroimaging studies of painful stimuli in humans have identified a network of brain regions that is more extensive than identified previously in electrophysiological and anatomical studies of nociceptive pathways. This extensive network has been described as a pain matrix of brain regions that mediate the many interrelated aspects of conscious processing of nociceptive input such as perception, evaluation, affective response, and emotional memory. We used functional magnetic resonance imaging in healthy human subjects to distinguish brain regions required for pain sensory encoding from those required for cognitive evaluation of pain intensity. The results suggest that conscious cognitive evaluation of pain intensity in the absence of any sensory stimulation activates a network that includes bilateral anterior insular cortex/frontal operculum, dorsal lateral prefrontal cortex, bilateral medial prefrontal cortex/anterior cingulate cortex, right superior parietal cortex, inferior parietal lobule, orbital prefrontal cortex, and left occipital cortex. Increased activity common to both encoding and evaluation was observed in bilateral anterior insula/frontal operculum and medial prefrontal cortex/anterior cingulate cortex. We hypothesize that these two regions play a crucial role in bridging the encoding of pain sensation and the cognitive processing of sensory input. *Hum Brain Mapp 27:715–721, 2006.*

Key words: cognitive; pain; fMRI; anterior insula; cingulate cortex

INTRODUCTION

Intensity is one of the most salient characteristics of pain. It is evaluated mainly by a person's subjective description of a private experience. The conscious perception of pain, however, does not always directly reflect incoming signals from primary sensory neurons [Melzack and Katz, 1994; Petrovic and Ingvar, 2002]; as incoming sensory input becomes part of conscious awareness, it undergoes extensive associative elaboration and modulation [Mesulam, 1998].

Conscious awareness of pain includes not only an appreciation of the quantitative and qualitative descriptive attributes of a noxious sensation but also the evaluation of the emotional meaning of the sensation. Previous literature sug-

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gests that the evaluation of a painful sensation involves at least two components. The first is an initial, automatic feeling of unpleasantness. The second, termed "secondary pain affect," represents the emotional response associated with the anticipation of future implications of pain [Gracely, 1992; Price, 2000; Price and Harkins, 1992]. An alternative interpretation is that the initial feeling of unpleasantness is encoded as part of the noxious sensation and that secondary pain affect is an outcome of the cognitive processing that occurs as part of the conscious awareness of the sensation.

The goal of this study was to test the hypothesis that spontaneous brain processing of variable intensities of noxious stimuli could be distinguished from the cognitive evaluation of pain intensity (pain rating). Previous reports led us to hypothesize that the brain regions that would be activated during the experience of different levels of pain would include contralateral primary somatosensory cortex (SI), bilateral secondary somatosensory cortex (SII), insular cortex/operculum, anterior cingulate cortex (ACC), and thalamus [Alkire et al., 2004; Bornhovd et al., 2002; Buchel et al., 2002; Peyron et al., 2000]. We will refer to these regions as the pain sensory intensity-encoding network. Cognitive evaluation of pain intensity (pain-rating tasks) requires mapping the nociceptive experience to some sort of semantic construct like a word or number on a scale and is only one part of the evaluative component of pain, which may include additional components such as pain quality, unpleasantness, and cognitive constructs such as the implication of pain [Price, 2000]. We hypothesized that the performance of a rating task requires the involvement of both brain regions supporting general cognitive evaluation tasks (i.e., deciding how loud a sound is or how bright a light is) as well as additional regions specific to evaluation of pain intensity. We specifically hypothesized that the anterior insular cortex, ACC, and dorsolateral prefrontal cortex would be activated during performance of a pain-rating task [Craig, 2002; Craig et al., 2000; Gollub et al., unpublished results; Maihofner et al., 2004].

SUBJECTS AND METHODS

Subjects

Sixteen right-handed subjects (8 males; mean age, 27 ± 6.0 years ± standard deviation [SD]) were recruited into this study as approved by the Human Research Committee of the Massachusetts General Hospital. All subjects gave written informed consent after the experimental procedures had been fully explained.

Experimental Procedures

Calibrated thermal pain stimuli were delivered to the right medial aspect of the forearm using a TSA-2001 Thermal Sensory Analyzer with a 3 cm × 3 cm probe (Medoc Advanced Medical Systems, Rimat Yishai, Israel) running proprietary computerized visual analog scale software [*COVAS*; Becerra et al., 1999; Peyron et al., 1999]. Thermal stimuli were 10 s in duration, including the 2.5-s ramp up and down from baseline, initiated from a baseline resting temperature of 32°C.

Subjects participated in two behavioral testing sessions followed by one functional magnetic resonance imaging (fMRI) scanning session. Each session was separated by a minimum of 1 week. The behavioral sessions were used to determine appropriate stimuli intensities, to minimize anticipatory anxiety, and to control for rating strategy and learning effects. The subjects were instructed in the use of 0–20 Sensory and Affective scales [Gracely et al., 1978a,b].

In the behavioral sessions, two heat pain stimulus intensities were selected for each subject; one to elicit responses in the strong range (HIGH PAIN; 14–17 on the Sensory Box Scale) and one to elicit responses in the mild to moderate range (LOW PAIN; 8–11 on the Sensory Box Scale). A warm, non-painful stimulus of 34°C (WARM) was used as a control for all subjects. To separate the sensory experience of the stimuli from the cognitive evaluative effort of the rating task, subjects were explicitly asked to focus their attention on their arm during each heat stimulus and then to wait for the scales to be displayed before performing the rating task.

In session 1, subjects first experienced an ascending series of calibrated heat stimuli (starting from 38°C and increasing by 1°C to 52°C or up to the subjects' tolerance). Temperatures that elicited subjective intensity ratings in the range of LOW pain and HIGH pain were selected for each subject. The ascending series was followed by randomized sequences of two repetitions of the three stimulus intensities (HIGH pain, LOW pain, and WARM). In session 2, the same randomized sequences were applied again and the temperature was adjusted if necessary to ensure that subjective ratings were in the desired range for each stimulus type.

In the fMRI scanning session, six different sequences of 12 stimuli trials were applied to six different regions of the right medial lower arm so that each region received one sequence. A sequence was applied during one functional run. A trial consisted of a presentation of a stimulus and a scale (Fig. 1). Three levels of stimuli (HIGH pain, LOW pain, and WARM) were presented during each stimulus sequence. Each level was presented four times and the order of presentation was ordered randomly. To begin each trial, a red fixation cross was displayed to cue the start of the stimulus administration. After the 10-s stimulus administration, the red fixation cross was replaced by a black fixation cross for 4 s, followed by one of the two types of scales (rating or control) for 10 s. Subjects were instructed to perform the appropriate scaling tasks as described below during the scale presentation. A black fixation cross was displayed during the intertrial interval, which varied with a mean interval of 6 s.

Subjects were instructed to focus on the stimulus but to wait until the scale was displayed to perform the poststimulus task. After half of the stimulus presentations, the 0–20 Sensory scale was displayed with a red pointer positioned at the middle number on the scale. In this condition, the subjects were required to rate the sensory intensity of the pre-

TABLE I. Brain areas activated during encoding of heat pain intensity

Comparison	Brodmann area	Z score	Cluster *P* value (corrected)	Voxels in cluster (n)	Peak coordinate (x,y,z)	Ratio
High > low pain	Left primary somatosensory cortex (1, 2)[a]	3.58	0.042	199	14, −42, 72	15/16
	Left postcentral cortex, SII (1,2,43)	4.97	0.000	325	66, −22, 22	15/16
	Right postcentral cortex, SII (1,2,43)	4.89	0.004	108	−66, −26, 20	15/16
	Left/right anterior cingulate/medial prefrontal cortex (24,32)	4.33	0.000	234	4, 2, 46	14/16
	Left/right lingualis gyrus (18)	4.24	0.000	285	20, −70, −2	13/16
	Left posterior/middle/anterior insular cortex	4.64	0.000	669	36, −20, 16	16/16
	Right middle/posterior insular cortex	6.58	0.039	55	−36, −16, 14	12/16
	Right middle insular cortex/frontal operculum	6.43	0.000	197	−52, 10, −4	15/16
	Right middle insular cortex/putamen	4.32	0.008	90	−32, 0, 2	12/16
	Right thalamus	6.84	0.000	386	−14, −8, 8	14/16
	Left thalamus	4.45	0.000	438	16, −14, 8	14/16
	Left/right cerebellum	4.79	0.000	339	0, −48, −26	15/16
	Right cerebellum	4.27	0.006	99	−8, −78, 18	13/16
Low pain > warm	No suprathreshold clusters[a]					

The threshold is set to voxel-wise $P < 0.0001$ uncorrected and cluster $P < 0.05$ corrected with 10 contiguous voxels. Ratio indicates the number of subjects to the total (N = 16) who showed activation ($P < 0.01$ voxels, uncorrected) in each region of interest. Peak coordinates refer to the MNI305 atlas.

[a] Original threshold of voxel-wise uncorrected $P < 0.001$ and cluster corrected $P < 0.05$ with 10 contiguous voxels.

SII, secondary somatosensory cortex; MNI, Montreal Neurological Institute.

ceding stimulus by pressing buttons with the left index and middle fingers to move the red pointer up and down (Fig. 1). In the other trials, the usual anchor words were omitted, replaced by a target bar pointing to one of the numbers on the scale (Fig. 1). To respond to this type of scale, subjects had to press a button to move the red pointer to the target number instead of giving their own rating of the intensity of the preceding stimuli. The choice of target numbers for the control task ensured that the two tasks required a comparable number of button presses. This target-matching task was used as control for the sensory intensity rating.

The order of two rating tasks and level of the previous noxious stimuli were ordered randomly and counterbalanced. Before scanning, subjects participated in a practice session, which included stimuli administration on the left arm and both scale tasks. Subjects were allowed to practice the tasks until they were confident about the process.

Functional MRI Data Acquisition and Analysis

All brain imaging was carried out with a three-axis gradient head coil in a 3 Tesla MRI system (Siemens Allegra; Siemens Medical Systems, Erlagen, Germany). Thirty axial slices (4-mm thick with 1-mm skip) parallel to the anterior and posterior commissure, encompassing the entire brain, were imaged with 2,000-ms repetition time (TR), 40-ms echo time (TE), 90-degree flip angle, and 3.13 × 3.13 mm in-plane spatial resolution. A high-resolution 3D magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence was also collected.

Preprocessing and statistical analysis were carried out using *SPM2* software (Wellcome Department of Cognitive Neurology). Preprocessing included motion correction, normalization to the MNI305 stereotactic space, and spatial smoothing with an 8-mm Gaussian kernel and default high-pass filtering to remove low-frequency noise. Global signal scaling was not applied to prevent spurious deactivations.

A random-effects analysis was carried out with *SPM2*. A separated general linear model (GLM) was specified for each subject with regressors for each of nine conditions tested: three intensity levels of HIGH pain, LOW pain, and WARM by three epochs of 10 s: administration of stimuli, sensory intensity rating, and matching target control. To examine the network that encodes pain intensity, we tested two contrasts for each subject: HIGH pain > LOW pain and LOW pain > WARM. Regions mediating the cognitive evaluation of heat pain intensity were identified by comparing the effects of the sensory rating task to the matching target control task for all noxious stimuli (HIGH and LOW pain intensity stimuli only), and also separately for each of the three stimulus intensities.

Group analysis was carried out using a random-effects model. Contrast images for each subject and each effect of interest were generated as described above. These contrast images were analyzed using a GLM to determine voxel-wise *t*-statistics. A one-way *t*-test was used to determine group activation for each contrast. Voxel-wise activation at $P < 0.001$ uncorrected and cluster activation $P < 0.05$ corrected with 10 contiguous voxels were considered to be statistically significant. In addition, a conjunction analysis was carried out to specifically identify brain regions activated by both sensory intensity encoding and evaluation.

RESULTS

Pain-Rating Data

Average ratings on the Sensory scale in response to the HIGH pain, LOW pain, and WARM intensities of the ther-

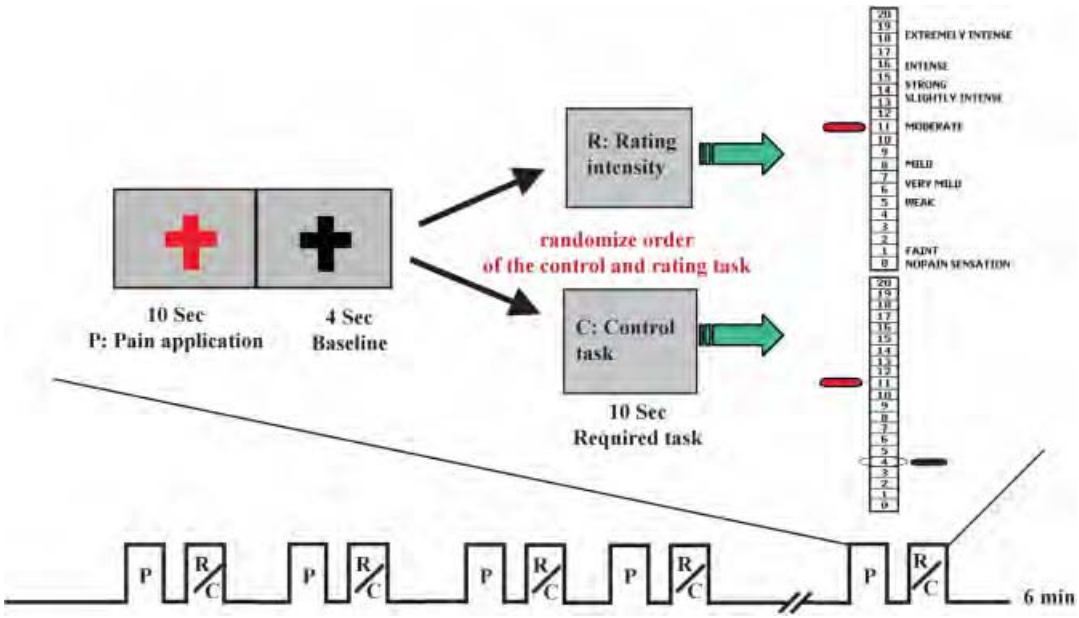

Figure 1.

Schematic representation of the experimental paradigm. Each 6-min scan was composed of a series of 12 pain stimuli trials followed by either a rating or control task in a single trial design. Each trial started with the fixation cross turning to red to cue the subject to attend to the administration of the thermal stimulus (10-s duration). There then was a 4-s delay during which a black fixation cross was displayed. This delay was followed by the display of either the Gracely Sensory Box scale with anchor words (Rating task) or of the same 0–20 number scale with a bar pointing to a circled target number (Control task). For either task, the subject used their left index and middle fingers to push buttons that moved a red pointer from midscale to the target number for the Control task or to the appropriate response number for the Rating task. The interval between two trials was randomized, with average of 6 s.

mal stimuli were within the intended ranges (mean ± SD) 14.8 ± 2.0, 8.5 ± 2.2, and 0.5 ± 0.7, respectively. In exit interviews, all subjects reported following the suggested strategy of focusing on the sensation during stimulus administration and waiting for the appearance of the scale to perform either the rating or target-matching task.

Functional MRI Results

Nociceptive and sensory intensity encoding

Table I shows significant regions of activation found in contrasts tested to elucidate the networks involved in sensory intensity encoding. Comparison between the two painful conditions (HIGH pain > LOW pain) yielded highly significant activations in the entire predicted network including bilateral insular and opercular cortices, ACC/medial prefrontal cortex (MPFC), SII, lingualis gyrus, thalamus, cerebellum and left SI (contralateral) in the arm region. These robust activations required an increase in the statistical threshold to voxel-wise uncorrected $P < 0.0001$ to separate clusters, but no new regions of activation were found even in the default threshold. The comparison of LOW pain > WARM provided no significant activations at the default threshold. At a lower threshold of voxel-wise uncorrected $P < 0.005$ with 10 continuous voxels, however, activations were observed in bilateral insular and frontal opercular cortices, and ACC/MPFC. These results indicate that the LOW pain stimuli elicited increases in brain activity throughout most of the network that were only slightly

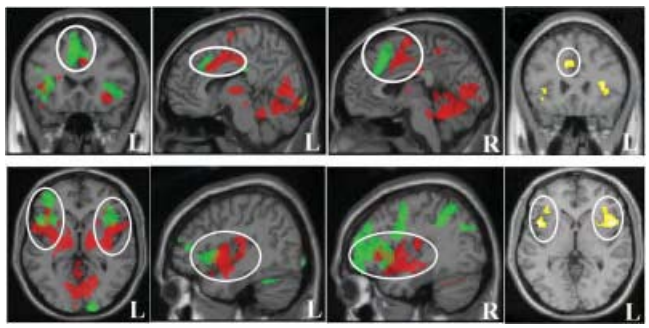

Figure 2.

Overlapping brain activations evoked by encoding of heat pain intensity (HIGH pain > LOW pain indicated by red color), cognitive evaluation of heat pain (PAIN rating > Control task indicated by green color) and the common regions of the two contrasts from conjunction analysis (indicated by yellow color). Threshold was set to $P < 0.001$ uncorrected with 10 continuous voxels. L, left; R, right.

TABLE II. Brain areas activated during cognitive evaluation of heat pain intensity

Comparison	Area (Broadmann area)	Z score	Cluster P value (corrected)	Number of voxels in cluster	Peak coordinate (x,y,z)	Ratio
Pain rating control task	Right middle/inferior/orbital prefrontal gyrus (9/10/11/45/46)	5.17	0.000	6830	−28, 52, 16	16/16
	Right anterior insular cortex/frontal operculum	5.09			−30, 20, 8	16/16
	Right/left medial prefrontal G./anterior cingulate cortex (24/32/6)	4.90			−12, 16, 56	14/16
	Right superior/inferior parietal lobule (7)	5.02	0.000	2666	−14, 74, 52	14/16
	Right angular gyrus (39)	4.31			−32, −80, 34	15/16
	Left anterior insular cortex/frontal operculum	4.33	0.000	930	42, 14, 2	15/16
	Left inferior prefrontal gyrus (45)/putamen	4.27			36, 32, 4	14/16
	Left occipital gyrus (17,18)	5.15	0.000	794	14, −98, −6	16/16

The threshold is set to voxel-wise uncorrected $P < 0.001$ and cluster $P < 0.05$ corrected with 10 continuous voxels. Ratio indicates the number of subjects of the total (n = 16) who showed activation (voxel-wise $P < 0.01$ uncorrected) in each region of interest.

greater than those in the WARM condition, whereas the HIGH pain stimuli elicited much greater increases in activation.

Cognitive pain intensity evaluation

Table II shows significant regions of activation for the contrast of the sensory rating task to the matching target control task for all noxious stimuli, which included bilateral anterior insula/frontal operculum, MPFC/ACC, right middle/inferior/orbital prefrontal gyrus, superior/inferior parietal lobule, angular gyrus, left inferior frontal gyrus, putamen, and occipital cortex. The separate analyses of the contrasts for the HIGH pain, LOW pain, and WARM trials reveal a strong influence of stimulus intensity on activity in this network (LOW pain rating > WARM rating > HIGH pain rating). Comparison of the rating to the control task after the LOW pain stimuli resulted in the most significant and widespread activation in regions, which include bilateral anterior insula and frontal operculum, right middle/inferior prefrontal gyrus, superior parietal cortex, inferior parietal lobule, MPFC/ACC, middle frontal gyrus, and left occipital cortex. Comparison of the rating to the control task after WARM stimuli trials revealed a significant activation only in bilateral occipital cortex at the threshold we set; lowering the threshold to $P < 0.005$ uncorrected with 10 continuous voxels revealed activation in bilateral occipital cortex, dorsolateral prefrontal cortex, insula, right superior parietal gyrus/precuneus, ACC/MPFC, and left precuneus. For the trials after HIGH pain stimuli, lowering the threshold to $P < 0.005$ uncorrected with 10 continuous voxels revealed activations in bilateral occipital cortex, left middle/inferior prefrontal gyrus, anterior insula, precuneus, superior/inferior parietal gyrus, right operculum/anterior insula and superior frontal gyrus. These results suggest that the activation patterns are quite similar for the ratings of different stimulus intensity levels, albeit with different significance.

Inspection of the statistical maps from individual subjects supports the results from the group analysis. Most subjects (at least 75%) showed significant activation in brain regions reported for the group analysis for conditions testing both sensory intensity encoding and cognitive pain intensity evaluation.

Overlap and difference between sensory intensity encoding and cognitive intensity evaluation

Figure 2 compares noxious sensory intensity encoding (HIGH pain > LOW pain) to cognitive sensory intensity evaluation (pain rating compared to target matching control task for all painful stimuli). Regions that were significantly activated in both contrasts include bilateral anterior insula and ACC/MPFC. Conjunction analysis using the minimum statistic compared to the conjunction null method [Friston et al., 2005; Nichols et al., 2005] was applied to investigate further the brain regions activated in common by the above two contrasts. The results showed the same regions of activation in bilateral anterior insula and ACC/MPFC (voxel-wise $P < 0.001$ uncorrected).

For sensory intensity encoding, the activation extended from anterior insula to the middle/posterior insula; for cognitive intensity evaluation, the activation extended from anterior insula to lateral and orbital (right) prefrontal area. In MPFC/ACC, the activation for sensory intensity encoding was localized posterior to the activation found for cognitive intensity evaluation.

The direct comparison of the above two contrasts to reveal differences between them yielded concordant results. Greater activations ($P < 0.001$ uncorrected and cluster activation $P < 0.05$ corrected with 10 contiguous voxels) were observed in right posterior insula/operculum (−40, −18, 4), right rostral ACC (−8, 54, −6), left posterior cingulate cortex (−10, −48, 34), right supramarginal gyrus (−46, −66, 34) and bilateral cerebellum (24, −18, −24; −14, −64, 14) during pain sensory encoding than during cognitive sensory inten-

sity evaluation. Greater activation was observed in left superior frontal gyrus (24, 6, 60), left middle frontal gyrus (32, 58, 14), left superior parietal lobule and precuneus (14, −72, 54), right occipital cortex (−14, −98, −4), and bilateral medial prefrontal cortex (2, 24, 48) during cognitive sensory intensity evaluation than during pain sensory encoding.

DISCUSSION

This study used fMRI to dissociate the neural processes of sensory encoding from the cognitive evaluation of heat pain intensity. The results confirm that the process of encoding pain sensation in the human brain uses multiple and parallel brain regions in both the lateral and medial pain systems, including the contralateral SI, bilateral insula/frontal operculum, MPFC/ACC, SII, and thalamus [Coghill et al., 1999]. These results are also consistent with recent studies that used the stimulus-response function to define the brain regions responsible for intensity encoding [Alkire et al., 2004; Bornhovd et al., 2002; Buchel et al., 2002].

Our sensory rating task identified a brain network active during the cognitive evaluation of pain intensity that includes bilateral anterior insula and frontal operculum, right middle/inferior prefrontal gyrus, superior parietal cortex, inferior parietal lobule, MPFC/ACC, middle frontal gyrus, and left occipital cortex. Importantly, the reactivation of the bilateral anterior insula occurred after the stimulus had ended, consistent with the fact that the sensory rating task required somatosensory imagery for retrieval of previous sensory information about both the pain to be rated and prior experiences for comparison. It also required matching the somatic sensation to a numerical scale, making a decision about a sensory rating, and more attention than that required for the control task. The brain regions in which we observed increased activity during pain intensity rating are similar to those activated by response selection, executive control, working memory, episodic memory, and perceptual and problem-solving tasks that involve high levels of mental effort [Duncan and Owen, 2000]. The activation in the occipital regions is most likely a consequence of the additional visual stimulation provided by the presence of the anchor words.

The results from the separate analysis of the ratings of LOW and HIGH pain stimulus intensities showed that less intense pain stimuli are more potent in the activation of the evaluative network. This finding is consistent with post-study oral reports from subjects indicating that stimuli in the mild to moderate range were the most difficult to rate whereas high-intensity stimuli were the easiest to rate. This self-report is supported by further analysis of the behavioral data, which shows that the LOW pain ratings are more variable than are the HIGH pain ratings within subjects. The mean and SD of the within-subject SDs are 2.6 ± 1.2 and 2.0 ± 1.1, for LOW and HIGH pain respectively. For 12 of 16 subjects, the LOW pain SD was greater. A paired *t*-test on the SDs for HIGH and LOW pain showed that the LOW pain SDs were significantly larger than that of HIGH pain ($P < 0.04$).

The different effects of task difficulty (less intense pain stimuli are more potent in the activation of the evaluative network whereas stronger pain stimuli are more potent in the activation of the encoding network) provide strong experimental support for the concept that sensory intensity encoding and cognitive evaluation of pain intensity involve different neural processing mechanisms.

In a recent fMRI study, Singer et al. [2004] reported anterior insula and ACC activation when female subjects experienced pain and when they witnessed a loved one experiencing pain. The two different conditions yielded overlapping areas of activation in the anterior insula and ACC that closely resemble what we observed in our study (see their Fig. 1 and our Fig. 2). The brain areas activated when subjects experienced their own pain match the brain areas activated in our subjects during pain encoding. In contrast, the areas activated by empathy with another's pain closely match areas activated by cognitive evaluation. Our interpretation of these results is that a common cognitive intensity evaluation process underlies assessment of the intensity of pain experienced by the self or by another person and that these processes are involved in the act of empathy.

A new finding from this study is the identification of overlapping regions in the bilateral MPFC/ACC and anterior insula/frontal operculum that are activated during both encoding and evaluation of pain intensity. Activation in both regions was extensive and the overlap was only partial. The ACC regions uniquely involved in evaluation of pain intensity were located in the cognitive subdivision of the ACC as defined by Bush et al. [2000] and anterior to those involved in sensory intensity encoding. We hypothesize that these two regions play a crucial role in bridging the sensory encoding of pain and the cognitive processing of sensory input.

The neuroanatomical literature provides evidence of the requisite pathways required to support the hypothesis of this bridging role for the anterior insula. The insular cortex is divided into four interconnected subdivisions; from rostral to caudal, they are: insular proisocortex, agranular subdivision, dysgranular subdivision, and the granular insular areas [Cipolloni and Pandya, 1999]. Agranular insula (primarily located in anterior portion of insula) receives projections from SI, retroinsular area, superior temporal sulcus, and the amygdaloid and entorhinal cortex and projects to frontal areas, retroinsular area, and SII [Augustine, 1996; Cipolloni and Pandya, 1999]. Further studies have shown that agranular insula also projects fibers into cingulate areas [Augustine, 1996]. All these innervations link the anterior insula with limbic, emotional arousal, and working memory system [Cahill and McGaugh, 1998]. This link provides the anatomical basis for the multiple functions of anterior insula.

A limitation in this study is the unknown extent to which we were able to separate the pain sensory encoding from cognitive sensory intensity evaluation. In this study, we made several efforts to separate these two procedures. First, we used a Gracely Sensory Box scale with anchor words (see

Fig. 1 for details of anchor words). This scale is more complicated than a simple 0–10 scale with no anchor words. Second, we trained the subject from the very beginning of their participation to feel the pain first and then to look at the scale to perform the ratings. Finally, during the fMRI scanning, the subjects only had to rate half of the total stimuli. This should have compelled them to follow the strategies we suggested and to pay attention to the pain and then wait for the scale to be displayed to do the sensory rating or button press to move the cursor to the target. All subjects reported that they followed these procedures. Nevertheless, subjects may confound the sensory encoding and cognitive evaluation to a certain extent.

In summary, we found two dissociated but overlapping brain networks involved in pain sensory intensity encoding and cognitive evaluation of pain intensity. The overlap of these two processes is localized to bilateral anterior insula and MPFC/ACC. A neural network that includes anterior insula/frontal operculum, MPFC/ACC, lateral/orbital prefrontal, and parietal cortex may represent a second level pain information processing circuit that supports the active, conscious cognitive evaluation of pain sensation.

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Cerebrospinal Fluid Corticotropin-Releasing Factor Concentration is Associated with Pain but not Fatigue Symptoms in Patients with Fibromyalgia

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Previous studies have identified stress system dysregulation in fibromyalgia (FM) patients; such dysregulation may be involved in the generation and/or maintenance of pain and other symptoms. Corticotropin-releasing factor (CRF) is the principal known central nervous system mediator of the stress response; however, to date no studies have examined cerebrospinal fluid (CSF) CRF levels in patients with FM. The relationship between CSF CRF level, heart rate variability (HRV), and pain, fatigue, and depressive symptoms was examined in patients with FM. Among participants ($n = 26$), CSF CRF levels were associated with sensory pain symptoms ($r = 0.574$, $p = 0.003$) and affective pain symptoms ($r = 0.497$, $p = 0.011$), but not fatigue symptoms. Increased HRV was also strongly associated with increased CSF CRF and FM pain. In multivariate analyses adjusting for age, sex, and depressive symptoms, the association between CSF CRF and sensory pain symptoms ($t = 2.54$, $p = 0.027$) persisted. Women with FM who reported a history of physical or sexual abuse had lower CSF CRF levels than women who did not report such a history. CSF CRF levels are associated with both pain symptoms and variation in autonomic function in FM. Differences in CSF CRF levels among women with and without a self-reported history of physical or sexual abuse suggest that subgroups of FM patients may exist with different neurobiological characteristics. Further studies are needed to better understand the nature of the association between CSF CRF and pain symptoms in FM.
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Keywords: fibromyalgia; corticotrophin-releasing factor; depression; abuse; heart rate variability

INTRODUCTION

Fibromyalgia (FM) is a common clinical syndrome defined by the presence of chronic widespread pain and increased tenderness to palpation (Wolfe *et al*, 1990). Recent studies have identified altered central nervous system pain processing in individuals with FM, supporting a neurobiological basis for the disorder (Gracely *et al*, 2002; Cook *et al*, 2004). However, the specific pathophysiologic mechanisms responsible for FM remain poorly understood.

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Some authors have proposed that disruptions in stress system function may be an important mechanism generating pain and other symptoms in FM (Chrousos and Gold, 1992; Crofford and Demitrack, 1996; Clauw and Chrousos, 1997). The principal components of the human stress response are the hypothalamic-pituitary-adrenocortical (HPA) axis and locus ceruleus/norepinephrine-sympathetic (LC-NE) system (Chrousos and Gold, 1992). Results of studies examining HPA axis function in patients with FM are inconsistent, with both HPA axis hypoactivity and hyperactivity identified (McCain and Tilbe, 1989; Griep *et al*, 1993; Crofford *et al*, 1994; Riedel *et al*, 1998; Catley *et al*, 2000). Autonomic nervous system function in patients with FM, reflected in both heart rate variability (HRV) and plasma catecholamine levels, suggests a central hypernoradrenergic state (Martinez-Lavin *et al*, 1998; Stein *et al*, 2004).

Corticotropin-releasing factor (CRF) is the principal known central nervous system mediator of the pituitary–

adrenal response to stress. CRF appears to be important to the pathophysiology of stress-related disorders such as post-traumatic stress disorder (PTSD) and depression; elevated levels of cerebrospinal fluid (CSF) CRF have been identified in both of these disorders (Bremner *et al*, 1997; Gold and Chrousos, 2002). Early life stress has also been associated with alterations in adult CSF CRF levels, in both preclinical and clinical studies (Carpenter *et al*, 2004; Heim *et al*, 2004), and recent study results indicate that that early life stress influences stress system function in adults with FM (McLean *et al*, 2005b; Weissbecker *et al*, 2005). In the single study assessing CRF levels in FM patients to date, Riedel *et al* (2002) found higher baseline serum CRF levels in FM patients *vs* healthy controls. To date, we are not aware of any studies that have examined CSF CRF concentrations among patients with FM.

In this study, we sought to identify the relationship between CSF CRF concentration and FM symptoms (ie pain, fatigue, and depressive symptoms), and between CSF CRF and measures of autonomic nervous system function (ie HRV) among patients with FM. We hypothesized that CSF CRF levels would be positively associated with pain and fatigue symptoms. We also hypothesized that increased CSF CRF levels would be associated with increased sympathetic nervous system activity among FM patients, given the identified association between CSF CRF and the LE-NE system (Palkovits, 1999). In addition, among women with FM, we explored the relationship between self-reported physical or sexual abuse and CSF CRF level.

PATIENTS AND METHODS

Patients

The study sample consisted of participants with FM ($n = 26$) recruited via local print advertisements and clinic samples. All participants underwent a detailed evaluation to exclude other medical conditions, including history and physical examination, and laboratory studies including CBC, serum electrolytes, BUN, Cr, TSH, sedimentation rate, and C-reactive protein. General exclusion criteria were as follows: (1) cigarette smoking; (2) substance abuse in the past 2 years; (3) medical conditions known to cause symptoms similar to FM symptomatology, including obesity ($BMI > 30\,kg/m^2$), autoimmune or inflammatory diseases, cardiopulmonary disorders, chronic asthma, uncontrolled endocrine, or allergic disorders (eg hypothyroidism, diabetes, allergic rhinitis), or malignancy; or (3) schizophrenia or major depression with suicidal ideation.

All participants were discontinued from psychoactive medications prior to study onset. Fluoxetine taper was completed at least 4 weeks prior to study initiation (two patients); other psychoactive medications were tapered off at least 2 weeks prior to study initiation. These other medications included other antidepressants (paroxetine (four patients), bupropion (one patient), trazodone (three patients), sertraline (two patients), nortriptyline (one patient), and amitriptyline (one patient)), other pain medications (methocarbamol (one patient), cyclobenzaprine (three patients), gabapentin (one patient), lidocaine patch (one patient), methadone (one patient), and oxycodone (one patient)), and benzodiazepines (lorazepam (one patient), diazepam (one patient), clonazepam (one patient), and zolpidem (one patient)). Nonsteroidal anti-inflammatory drugs were discontinued at least 3 days prior to the study (nine patients).

All participants received specialized evaluation to determine if they met the 1990 American College of Rheumatology criteria for the classification of FM (Wolfe *et al*, 1990). Patients who reported a history of FM but did not meet ACR criteria at the time of the study were excluded. The presence of psychiatric disorders was assessed using the Composite International Diagnostic Interview (Wittchen, 1994). In addition, participants were asked if they had ever been the victim of physical or sexual abuse. No specific definition of physical or sexual abuse was provided. If a participant did report abuse, they were asked the age at which the physical or sexual abuse occurred or began.

Self-Report Instruments

Participants completed the following self-report instruments, each of which was chosen based on its psychometric properties and applicability to the FM population:

Short-Form of the McGill Pain Questionnaire: This SF-MPQ questionnaire has been extensively evaluated and contains 15 pain adjectives (Melzack, 1987). A sensory score is obtained by summing 11 of the items, an affective score is obtained by summing the remaining four items, and a total score is obtained by summing all of the items.

The Multidimensional Fatigue Inventory (MFI): The MFI is a 20-item instrument that assesses the following dimensions of fatigue: general fatigue, physical fatigue, mental fatigue, reduced activity, and reduced motivation. It has been validated among multiple patient populations, including individuals with chronic fatigue syndrome (CFS) (Smets *et al*, 1995).

The Center for Epidemiological Studies Depression Scale (CES-D): The CES-D is a 20-item measure that assesses multiple components of depressive symptomatology: depressed mood, feelings of guilt and worthlessness, feelings of helplessness and hopelessness, loss of appetite, sleep disturbance, and psychomotor retardation. The CES-D has demonstrated strong associations with other depressive symptom measures (Radloff, 1977) and has been validated in pain populations (Geisser *et al*, 1997).

Procedures

The study protocol included a 2-day in-patient evaluation conducted in the Georgetown University Medical Center's General Clinical Research Center (GCRC). Menstruating women were scheduled to undergo study evaluations during days 3–7 of the follicular phase of their menstrual cycle. The in-patient GCRC evaluation began at 1800 hours. Participants initially completed self-report questionnaires, then had a Holter monitor (ACS Holter, Ontario, CA) placed at 2000 hours. This Holter monitor was worn overnight and during day 1 of the GCRC protocol. This protocol included several participant stressors, including evoked pain testing, cognitive testing, and exercise testing via cycle ergometer. The Holter monitor was removed at 1700 hours, after completion of the day's protocol. Participants then spent another night in the GCRC, followed by a lumbar puncture

performed at 0830 hours the next morning by a board-certified anesthesiologist. Participants had nothing to eat or drink after midnight prior to the test. The study protocol was approved by the Georgetown University Institutional Review Board, and all participants gave informed consent prior to protocol enrollment. Participants were compensated $425.

Holter monitor data was used to assess autonomic nervous system function via HRV. Autonomic dysfunction has been identified in patients with FM (Radulovic *et al*, 1995), and multiple lines of evidence suggest an association between CRF levels and LC-NE/autonomic nervous system function (Gold and Chrousos, 2002). HRV represents the beat-to-beat variation in consecutive R–R intervals. Fluctuations over time in these intervals are mediated by autonomic inputs to the sinus node, and measures of HRV represent a surrogate measure of autonomic nervous system modulation. HRV was assessed across the different domains of the heart rate power spectrum (frequency domain analysis), including power in the ultra-low- (ULF), very low- (VLF), low- (LF), and high-frequency (HF) bands. The LF to HF power ratio was also calculated. Power in the HF band (0.15–0.4 Hz) largely reflects respiration-mediated vagal contributions to the beat-to-beat variations in heart rate (Stein and Kleiger, 1999). The LF band is thought to be modulated by both the sympathetic and parasympathetic nervous systems. It is measured between 0.04 and 0.15 Hz (Stein and Kleiger, 1999). Even slower modulations of heart rate are reflected in the VLF domain (0.0033–0.04 Hz). VLF was long believed to represent the influence of the peripheral vasomotor and renin–angiotensin systems (Akselrod *et al*, 1981); however, recent studies using pharmacological blockade support a strong contribution of the parasympathetic nervous system to VLF (Taylor *et al*, 1998). The remainder of the power spectrum is subsumed by the ULF domain, which reflects all variance below 0.0033 Hz, and consists of mainly circadian rhythms. All of these indices together represent the total power, which is the sum of all the variance in the heart period signal. The LF/HF ratio is a rough estimate of fluctuations in the balance between the sympathetic and parasympathetic nervous systems (Stein and Kleiger, 1999).

Three samples of CSF, 3 cm^3 each, were obtained via lumbar puncture. The third sample was immediately spun, aliquoted, and stored at $-70^{\circ}C$ for later batch analysis of CSF CRF. Concentrations of CSF CRF were measured using radioimmunoassay (Peninsula Laboratories, San Carlos, CA; detection limit, 1 pg/100 μl).

Statistical Analysis

All study data were entered onto a secure database via double data entry. CSF CRF levels among male and female participants were compared via the Wilcoxon–Mann–Whitney test. Partial correlations between CSF CRF and demographic, history, and symptom characteristics and autonomic nervous system function were calculated using Spearman's rank correlation, adjusting for age and sex. Multiple linear regression analysis was used to assess the amount of variance in CSF CRF explained by demographic and symptom characteristics and autonomic nervous system function, and to assess the association between pain symptoms and CSF CRF, adjusted for age, sex, and depressive symptoms. In addition, among women with FM, the association between self-reported abuse history and CSF CRF was assessed, as well as the amount of variance in CSF CRF explained by abuse history, depressive symptoms, and McGill sensory subscale score.

Possible interactions were assessed in preliminary models. If no significant interaction was present, the interaction term was excluded from the final model. The variance in the dependent variable explained by the regression model was assessed via adjusted R^2. Goodness of fit and model aptness were evaluated via residual analysis. All regression models were evaluated for normality and other diagnostic issues. For Tables 4 and 5, the McGill pain scales and CSF CRF significantly deviated from normality and were symmetrized by using a natural log transformation. Statistical analyses were performed using SPSS software (SPSS Inc., Chicago, IL).

RESULTS

Participant Characteristics

Participant demographic and symptom characteristics and CSF CRF levels are shown in Table 1. CSF CRF levels were higher in males than in females ($p = 0.03$). Consistent with prior reports (Clauw and Chrousos, 1997), CFS defined via the CDC criteria (Fukuda *et al*, 1994) often coincided with FM (22 of 26 patients; 85%).

CSF CRF Levels and FM Symptom Characteristics and Autonomic Nervous System Function

Table 2 presents the partial correlations between CSF CRF and FM symptom characteristics and autonomic nervous system function, adjusted for age and sex. Increased CSF CRF was strongly associated with increased pain symptoms, but not fatigue symptoms. CSF CRF was also strongly associated with autonomic nervous system function, particularly the LF portion of the spectrum, which is consistent with increased sympathetic activity. Sixty-six percent of the variation in CSF CRF was accounted for by a regression model containing McGill pain sensory score, LF HRV, age, gender, and depressive symptoms (Table 3).

To further examine the relationship between CSF CRF and patient pain and depressive symptoms, multiple linear regression analyses were performed using McGill sensory and affective subscale scores as dependent variables (Table 4). The strong association between McGill sensory and affective subscale scores and CSF CRF persisted after adjustment for depressive symptoms. These two models accounted for 45 and 24% of the variation in McGill sensory and affective subscale scores, respectively.

Self-Reported History of Physical or Sexual Abuse and CSF CRF among Women with FM

During the initial screening examination, participants were asked if they had ever been physically or sexually abused, and, if so, the age at which any such abuse occurred or

Table 1 Characteristics of Study Participants ($n = 26$)

Characteristic	Mean (SD) or N (%)
Age (mean, SD)	43 (9)
BMI (mean, SD)	26.4 (4)
Male (*n*, %)	10 (38)
Race (n, %)	
White	13 (52)
Black	7 (28)
Hispanic	3 (12)
Other	3 (12)
Symptom score (mean, SD)	
McGill sensory	10 (6)
McGill affective	3 (2)
MFI—general fatigue	16.2 (2)
MFI—mental fatigue	14.2 (4)
MFI—physical fatigue	14.2 (4)
MFI—reduced activity	11.8 (5)
MFI—reduced motivation	10.5 (4)
CES-D	16.4 (9)
Education (n, %)[a]	
High school	1 (4%)
Some college	11 (42%)
College graduate	9 (35%)
Postgraduate degree	4 (15%)
CSF CRF level (mean, SD (pg/ml))	
All participants ($n = 26$)	31.8 (12.5)
FM men ($n = 10$)	38.9 (14.0)
FM women reporting abuse ($n = 7$)	25.4 (11.5)
FM women not reporting abuse ($n = 9$)	35.0 (12.4)

BMI, body mass index; MFI, multidimensional fatigue inventory; CES-D, Center for Epidemiologic Studies-Depression Scale.
[a]Education information missing on one participant.

began. Seven of the 16 women with FM reported an abuse history. Five of these women stated that the abuse began between 5 and 13 years of age, and the other two women reported abuse as adults. Two of the women who reported abuse during their preteen years met CIDI criteria for PTSD. Among women with FM in our sample, abuse history was not correlated with number of depressive symptoms ($r = 0.14$, $p = 0.66$). As shown in Figure 1, women reporting a history of physical or sexual abuse had a significantly lower CSF CRF than women not reporting such a history (22 *vs* 32 pg/ml, $P = 0.012$). This group difference persisted when the FM woman not reporting abuse with the highest CSF CRF value (50 pg/ml) was removed ($p = 0.020$). Among women with FM, 64% of the variance in CSF CRF was accounted for by a model that contained McGill pain sensory score, self-reported abuse history, and depressive symptoms (Table 5).

Table 2 Partial Correlation between CSF CRF and Fibromyalgia Symptom Characteristics and Autonomic Nervous System Function, Adjusted for Age and Sex

Characteristic	*r*	*p*-value
Symptom score		
McGill sensory	0.574	0.003
McGill affective	0.497	0.011
MFI—general fatigue	0.163	0.436
MFI—mental fatigue	0.067	0.752
MFI—physical fatigue	0.322	0.117
MFI—reduced activity	0.327	0.111
MFI—reduced motivation	0.346	0.090
CES-D (SD)	0.458	0.021
Autonomic measures		
TP (ms^2)	0.497	0.028
HF (ms^2)	0.579	0.012
LF (ms^2)	0.656	0.003
VLF (ms^2)	0.456	0.057
LF/HF ratio	−0.256	0.305

CSF CRF, cerebrospinal fluid corticotrophin-releasing factor; MFI, multidimensional fatigue inventory; CES-D, Center for Epidemiologic Studies-Depression Scale; TP, total power heart rate variability; HF, high-frequency heart rate variability; LF, low-frequency heart rate variability; VLF, very-low-frequency heart rate variability.

Table 3 Association between CSF CRF and Patient Characteristics and Autonomic Nervous System Function

Dependent measure	Independent variable	Beta	t	*p*-value
CSF CRF	Age	0.359	2.034	0.067
	Sex	0.387	1.955	0.076
	McGill sensory	0.456	2.545	0.027
	CES-D	0.278	1.796	0.100
	LF (ms^2)	0.555	3.049	0.011

CSF CRF, cerebrospinal fluid corticotrophin-releasing factor; CES-D, Center for Epidemiologic Studies-Depression Scale; LF, low-frequency heart rate variability.

Table 4 Association between Patient Pain Symptoms and CSF CRF, Adjusted for Age, Sex, and Depressive symptoms

Dependent measure	Independent variables	Beta	t	*p*-value
McGill sensory	Age	−0.189	−1.138	0.268
(Natural Log)	Sex	-0.686	−3.604	0.002
	CES-D	−0.003	−0.014	0.989
	CSF CRF	0.559	2.876	0.009
McGill affective				
(Natural Log)	Age	−0.302	−1.629	0.119
	Sex	−0.382	−1.794	0.088
	CES-D	0.048	0.246	0.808
	CSF CRF	0.557	2.559	0.019

CES-D, Center for Epidemiologic Studies-Depression Scale; CSF CRF, cerebrospinal fluid corticotrophin-releasing factor.

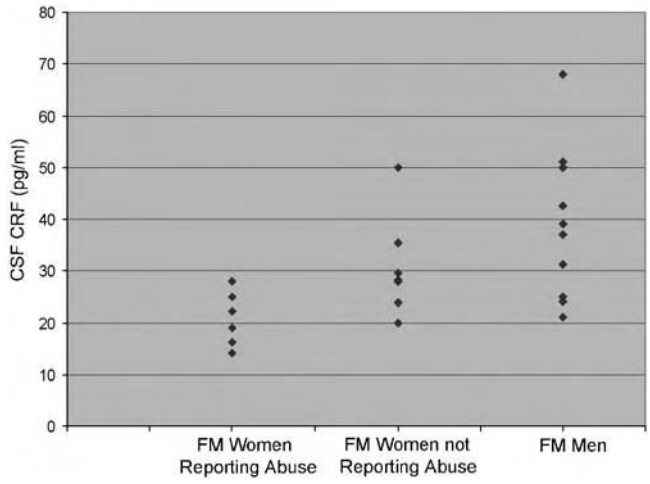

Figure 1 CSF CRF level among FM women reporting and not reporting a history of abuse, and among men with FM.

Table 5 Association between CSF CRF and Self-Reported Abuse History, Depressive Symptoms, and Pain Symptoms among Women with Fibromyalgia

Dependent measure	Independent variable	Beta	t	*p*-value
CSF CRF	Abuse history	0.392	3.26	0.009
(Natural Log)	CES-D	0.016	2.48	0.033
	McGill sensory	0.019	1.898	0.087

CSF CRF, cerebrospinal fluid corticotrophin-releasing factor; CES-D, Center for Epidemiologic Studies-Depression Scale.

DISCUSSION

Among patients with FM, pain symptoms, but not fatigue symptoms, were strongly associated with CSF CRF concentration. This association was not accounted for by differences in age, sex, or depressive symptoms. FM pain symptoms were consistently more strongly associated with CSF CRF than were depressive symptoms. Increased HRV, in a manner consistent with elevated sympathetic nervous system activity, was also associated with increased CSF CRF and with pain symptoms. This association is consistent with the interconnected function of the CRF and LC-NE systems (Arlt *et al*, 2003).

There are three possible explanations for the association between CSF CRF and pain symptoms in patients with FM: CRF may be altered as a consequence of chronic stress caused by pain, CRF may be involved in the generation of pain symptoms, and/or CRF may be a 'third variable' that is altered because of the dysfunction of other central processes directly involved in the generation of FM pain. Numerous animal studies have demonstrated that CRF is capable of influencing nociception (Lariviere and Melzack, 2000), but there is little direct evidence to distinguish between these alternatives. Indirect evidence that stress system dysregulation (due to genetic or environmental influences) is involved in the pathogenesis of FM (McLean *et al*, 2005a) suggests that CRF levels may be altered by mechanisms other than the chronic stress of illness alone. The results of this study, combined with the findings in a recent study that elevated cortisol levels are associated with FM pain but not fatigue symptoms on a momentary basis (McLean *et al*, 2005b), also support the hypothesis that HPA axis hyperactivity is linked specifically to FM pain.

The relationship between CSF CRF levels and the activity of CRF-secreting neurons in the hypothalamic paraventricular nucleus (which influence pituitary–adrenal function) is not well understood. Evidence indicates that the great majority of CSF CRF originates from outside the hypothalamus (Garrick *et al*, 1987; Kalin *et al*, 1987; Kling *et al*, 1994), and CSF CRF levels do not correlate well with adrenocorticotropin and cortisol levels on a momentary basis (Geracioti *et al*, 1997). However, in rodent models lesioning the paraventricular nucleus decreases CSF CRF by 50–60% (Hong *et al*, 1995; Gold and Chrousos, 2002). In humans, elevated CSF CRF levels have been found to be associated with a blunted adrenocorticotropin response to exogenously administered CRF (Newport *et al*, 2003). This blunted adrenocorticotropin response is believed to be due to chronic hyperactivity of CRF-secreting paraventricular neurons, suggesting that CSF CRF may be associated with paraventricular nucleus CRF secretion over the long term (Newport *et al*, 2003).

FM women in our sample who reported a history of physical or sexual abuse had significantly lower levels of CSF CRF than those who did not report such a history. This finding is consistent with that of Carpenter *et al* (2004), who found that perceived life stress during the preteen years was associated with decreased CSF CRF. The influence of self-reported childhood abuse has only recently been assessed in studies of stress axis function in FM (McLean *et al*, 2005b; Weissbecker *et al*, 2005), despite the fact that FM patients are often recruited for research studies from tertiary care clinic populations, where the prevalence of self-reported abuse is often 50% or more (Taylor *et al*, 1995; Goldberg *et al*, 1999; Carpenter *et al*, 2004). These recent studies describe relatively low cortisol levels in FM patients reporting a history of childhood abuse, and relatively high levels in those not reporting a history (McLean *et al*, 2005b; Weissbecker *et al*, 2005). These data and the present study suggest that FM patients with a history of abuse may have relatively low levels of basal CSF CRF and cortisol secretion, whereas those without such a history may have relatively high levels.

Some of the inconsistencies of the HPA literature regarding FM may be due to the failure to adjust for the confounding influence of abuse and other forms of early life stress. The results of this study suggest that important subgroups of FM patients may exist depending on early life stress exposure. Such neurobiological differences may also influence treatment response, thus early life stress exposure may be an important domain to include in both FM assessment and intervention studies.

The results of this study also suggest that the presence and severity of chronic pain may be another important domain to assess in CRF studies of other stress-related disorders such as depression and PTSD. The relationship between pain and depression is complex (Campbell *et al*, 2003). An average of 65% of patients with major depression have some degree of comorbid pain symptoms (Bair *et al*, 2003). Similarly, 20–30% of outpatient civilian samples with

PTSD (Hubbard *et al*, 1995; Amir *et al*, 1997; Beckham *et al*, 1997) and 80% of combat veterans with PTSD (Beckham *et al*, 1997) have comorbid chronic pain. If there is also an association between pain and CSF CRF in these populations, this could account for some of the previously inconsistent results of studies examining CSF CRF concentration in these disorders.

The purpose of this study was to compare FM patient symptoms and CSF CRF levels, no matched control group was employed. Previous studies utilizing control groups have reported mean CSF CRF levels of 22–25 pg/ml among controls (Bremner *et al*, 1997; Carpenter *et al*, 2004; Williams *et al*, 2004). In the present study, men and women with FM not reporting an abuse history had CSF CRF levels substantially higher than this (38.9 and 35.0 pg/ml, respectively), suggesting that FM in patients without a history of significant early life stress may be characterized by elevated CSF CRF levels.

This study has a number of limitations that should be considered when interpreting the results. First, the fact that our FM patients were recruited at a tertiary referral center, consented to a GCRC protocol involving a lumbar puncture, and were reimbursed for their participation suggests that they may not be typical of the FM population in the community. In addition, study participants were asked if they had ever been physically or sexually abused, but were not asked behaviorally specific questions (eg 'did anyone ever touch your genitals when you didn't want them to'). The definition of abuse in this study was thus not specifically defined, and relied solely on participants' own label of their past experience. This kind of 'label' only abuse assessment is a relatively insensitive method of identifying abuse victims compared with asking behaviorally specific questions, because a significant number of victims do not label their experiences as 'abuse' (Hamby and Gray-Little, 2000; Fricker *et al*, 2003). Thus, our method of identifying abuse history may not have identified all participants with an abuse history in the study. Error in classification would underestimate true differences between those with or without self-reported abuse, and could increase the inaccuracy of regression model estimates. However, the self-reported abuse prevalence among FM patients in our sample is similar to that reported in other FM tertiary care populations (Taylor *et al*, 1995; Goldberg *et al*, 1999; Carpenter *et al*, 2004), and the validity of the brief self-report measure used in the study is supported by the lower CSF CRF levels found among those reporting abuse, which is consistent with the known biological affects of early life stress (Carpenter *et al*, 2004; Heim *et al*, 2004).

Results of this study indicate that current pain symptoms are associated with CSF CRF concentration among patients with FM. These data support the hypothesis that abnormalities in the 'stress response' are associated with pain symptoms in FM, and that this association is not explained by the known associations between stress response function and depressive symptoms. Early life stress also appears to influence adult CSF CRF levels; how the association between and CSF CRF level and FM pain symptoms is influenced by early life stress is not known. Further studies examining the relationship between CSF CRF and pain symptoms in FM and in other chronic pain and psychiatric disorders are needed, to confirm this finding and to determine the mechanisms involved in the association between CRF and pain.

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Psychophysical Elements of Place and Modality Specificity in the Thalamic Somatic Sensory Nucleus (Ventral Caudal, Vc) of Awake Humans

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Psychophysical Elements of Place and Modality Specificity in the Thalamic Somatic Sensory Nucleus (Ventral Caudal, Vc) of Awake Humans

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[1]*Department of Neurosurgery, Johns Hopkins Hospital, Baltimore Maryland;* [2] *Department of Anesthesiology, M.D. Anderson Medical Center, Houston, Texas; and* [3]*Departments of Internal Medicine-Rheumatology and Neurology, University of Michigan Health System and Ann Arbor Veterans Affairs Medical Center, Ann Arbor Michigan*

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Patel, S., S. Ohara, P. M. Dougherty, R. H. Gracely, and F. A. Lenz. Psychophysical elements of place and modality specificity in the thalamic somatic sensory nucleus (ventral caudal, Vc) of awake humans. *J Neurophysiol* 95: 646–659, 2006. First published September 28, 2005; doi:10.1152/jn.00756.2005. Discrete anatomic structures in the monkey somatic sensory thalamus may segregate input arising from different peripheral receptors and from different parts of the body. It has been proposed that these structures serve as components of modality- and place-specific pathways from the periphery to the cortex. We now test this hypothesis by examining the modality- and place-specific segregation of sensations at sites where microstimulation (μA currents) within the region of ventral caudal (Vc; human principal somatic sensory nucleus) evokes somatic sensations. Microstimulation was delivered in an ascending staircase protocol consisting of different numbers of pulses (4–100) presented at different frequencies (10–200 Hz) during awake thalamic surgery for movement disorders. The results demonstrate that the part of the body where microstimulation evoked sensation (projected field) and the descriptors of nonpainful sensations were usually uniform across the staircase. These results strongly support the existence of psychophysical elements of place and modality specificity in the Vc thalamus. The proportion of sites at which the sensation included more than one part of the body almost always stayed constant over current intervals (plateaus) of 10 μA. Similar plateaus were not found for sites with more than one descriptor, suggesting that elements of modality-specificity are smaller than and located within those for place-specificity. The intensity of sensations varied with the number of stimulation pulses for mechanical/tingle and cool sensations. The results provide strong evidence for psychophysically defined elements that are responsible for modality specificity of nonpainful sensations, place specificity, and intensity coding of somatic sensation in the human thalamus.

INTRODUCTION

Distinct thalamic anatomic structures may subserve different modalities of somatic sensation as components of segregated pathways from the periphery to the cortex (Johnson 2001; Kaas and Pons 1988). For example, anterior-posteriorly oriented rods have been described within the monkey thalamic principal sensory nucleus (ventral posterior, VP) (Jones et al. 1982; Rausell et al. 1992). These rods are anatomically defined by the terminal arbors of axons from the medial lemniscus (Hirai et al. 1988; Rausell and Jones 1991) and are physiologically defined by neuronal responses to innocuous stimulation (Jones et al. 1982; Kaas et al. 1984; Lenz et al. 1988b; Morrow and Casey 1992; Tremblay et al. 1993). Thalamo-cortical fibers parallel the rod from which they originate (Landry and Deschenes 1981) and terminate in cortical columns (Jones et al. 1982), consistent with the modality-specific organization in the primary sensory cortex (Jones et al. 1982; Kaas 1983; Rausell et al. 1992). Similarly, thalamic rods subserve different cutaneous structures (e.g., glabrous or hairy skin) consistent with the place-specific organization in the primary sensory cortex (Jones et al. 1982).

The primate spinothalamic tract (STT) may also terminate in discrete anatomic structures. Anatomic studies after cordotomy demonstrate that the STT terminates as "disseminated bursts" of axonal arbors in monkey VP and in the corresponding human nucleus (ventral caudal, Vc) (Apkarian and Shi 1994; Mehler 1962; Mehler et al. 1960; Rausell et al. 1992; Willis et al. 2001). These disseminated bursts may correspond both to the location of neurons responding to thermal or noxious stimuli and to the calbinden staining matrix that is located between rods (Apkarian and Shi 1994; Bushnell et al. 1993; Casey and Morrow 1987; Lee et al. 1999; Rausell and Jones 1991). The STT also terminates in the area below and behind Vc, where stimulation evokes thermal and pain sensations (Davis et al. 1999; Ohara and Lenz 2003). These results suggest the hypothesis that different modalities of cutaneous sensation might be relayed through psychophysically defined modality- and place-specific elements in Vc.

The existence of such elements and psychophysics of their activation has not previously been reported. We have now studied the sensations evoked by activation of these thalamic elements in humans using microstimulation in an ascending staircase protocol. Each step along the staircase is a stimulus train characterized both by the number of pulses (4, 7, 20, 50, or 100) and by the stimulus frequency (10, 20, 38, 100, or 200 Hz) (see Fig. 3). We tested a corollary of the preceding hypothesis, that the same modality of sensation will be evoked at any site by different steps along the staircase (modality consistency). Further, we tested the corollary that the evoked sensations at different steps along the staircase at a site will be located on the same part of the body (place consistency). The results provide strong psychophysical evidence for place- and nonpainful modality-specific representation of somatic sensation in the thalamus of awake humans.

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METHODS

These studies were carried out at the Johns Hopkins Hospital during the thalamic exploration that preceded thalamotomy or implantation of deep brain stimulating electrodes for the treatment of movement disorders (Garonzik et al. 2002). The protocol used in these studies was reviewed and approved annually by the Institutional Review Board of the Johns Hopkins University. All subjects signed an informed consent for these studies. No patient had abnormalities on standard sensory testing (Lenz et al. 1993) or preoperative MRI scans or had a diagnosis of chronic pain (Merskey 1986).

In the present study, subjects were operated on for treatment of movement disorders (men: 32, women: 18) including: 35 with essential tremor, 11 with Parkinson's tremor, and 4 with dystonia (Watts and Koller 1998). Somatic sensations were evoked by thalamic microstimulation (110 sites) with different stimulus trains, each defined by the number and frequency of pulses as steps along an ascending staircase (see Fig. 3). The present population was a subset of the 116 patients (124 thalami) in which microstimulation at 300 Hz evoked mechanical or movement sensations (Ohara et al. 2004) and thermal or pain sensations (Ohara and Lenz 2003). We have previously described the response to stimulation along the staircase at sites where pain was evoked in both the present population and a population of patients with chronic pain (Lenz et al. 2004).

Recording protocols

Physiologic exploration of the thalamus was carried out as an image-guided stereotactic procedure under local anesthetic using the Leksell frame (Lenz et al. 1993). The stereotactic coordinates of the anterior commissure (AC) and posterior commissure (PC) were determined by computer-assisted tomography or magnetic resonance imaging and were used to estimate the location of the Vc (Hua et al. 2001). Specifically, the sagittal sections of a standard atlas (Schaltenbrand and Bailey 1959) were translated to match the subject's ACPC line and so form a map of the subject's thalamus. The 13.5-mm lateral section was a sagittal map of the subject's thalamus that was used as the first estimate of nuclear location (Fig. 1*A*).

Physiological corroboration of anatomical loci was then performed under local anesthesia (i.e., subject fully conscious) by using single-unit recording and microstimulation (Lenz et al. 1988a,b). EMG activity was routinely monitored in four muscles on the contralateral arm to assess involuntary movements at the time of the sensory examination (Lenz et al. 1988c). The first trajectory targeted Vc because the response of neurons in this region to somatosensory stimulation was the most reliable physiologic landmark with which to guide the operation (Lenz et al. 1995b).

As illustrated in Fig. 1, sites were explored starting 1 cm above the target and were characterized by the location of the sensation evoked (projected field) by threshold microstimulation (μA current levels). Projected fields at a stimulation site were characterized by inclusion of one or more parts of the body progressing from medial (intra-oral) to lateral (toes; Table 3) (Lenz and Byl 1999). Single neurons were characterized by their spontaneous activity and by their response to innocuous and noxious mechanical and temperature stimuli (Lee et al. 1999). Neurons responding to stimulation of the skin were termed cutaneous neurons, whereas deep neurons were those that responded to stimuli applied to deep structures (joints, ligaments, etc.) but not to stimulation of skin deformed by these stimuli.

The core region of Vc was defined as region where the majority of neurons responded to innocuous cutaneous stimulation (Fig. 1) (Ohara and Lenz 2003; Ohara et al. 2004). The analysis of thalamic location was based on the borders of the core as illustrated in Fig. 1*B*. The ventral border of the core of Vc is indicated by the dashed line parallel to AC-PC line and is determined by the location of the most ventral neuron responding to innocuous, cutaneous stimulation (*neuron 48* in Fig. 1*C*). The dotted and solid lines perpendicular to the AC-PC line are the anterior and posterior (Z axis) borders of Vc, respectively. These lines are determined by the location of the most anterior neuron (33) and posterior neuron (48) responding to innocuous, cutaneous stimulation.

Microstimulation protocol

Microstimulation at 300 Hz was delivered in trains of ~1 s duration by using a biphasic square-wave consisting of a 0.2-ms anodal pulse followed in 0.1 ms by a cathodal pulse of the same duration and magnitude. Stimulation was carried out at 40 or 50 μA at sites located at regular intervals along the trajectory until a sensory response was evoked.

At each stimulation site, subjects were first asked whether they felt anything (Lenz et al. 1993, 1998). If a sensation was evoked, then a threshold was established by increasing and decreasing the stimulation current. If no sensation was evoked at 40 or 50 μA, then a no response (NR) was entered at that site. Sites were named by the first sensation described by the subject so that a site where microstimulation evoked a cool sensation was termed a cool site. The current threshold was established by lowering the current for successive stimuli until a sensation was no longer evoked. The current was then increased until a sensation was evoked again. This procedure was often repeated to verify the threshold. The sites where microstimulation evoked sensations were plotted with respect to the borders of core region of Vc in the parasagittal plane (Fig. 1).

The constant location of the electrode during the stimulation protocol was confirmed at each site. Before and after the stimulation protocol, 300-Hz stimulation was applied at the initial threshold to confirm that the projected field was unchanged. During recording, we compensated for movement of the electrode in the brain by making small electrode movements ($<$100 μm) to keep the size of the action potential constant. In addition, the receptive field, and the size and shape of the action potential were checked for consistency before and after microstimulation at each site. Nevertheless, we have no anatomic measure of the error in our estimate of the location of the electrode.

Psychophysical protocols

The patient was questioned to determine the location of the microstimulation-evoked sensation (projected field). The microstimulation-evoked sensation was described using the questionnaire (Fig. 2) during repeated stimulation. The patient was asked (*question 1*) to decide if the sensation was natural by identifying the stimulus and judging if the stimulus was "something that you might encounter in everyday life." The patient was then asked to decide if the sensation was located either on the surface of the skin or below the surface of the skin, or both (Fig. 2, *question 2*). Neither of these questions was a forced choice.

If the sensation was nonpainful (*question 3*), the patient chose a descriptor(s) from the upper list under heading 4, labeled "nonpainful." If the sensation was painful, the patient chose a descriptor(s) from the lower list labeled "painful." In this section, the patient was asked first to identify which of the categories of sensation applied (e.g., mechanical, movement, etc.) and then to identify descriptors within the chosen category. Patients were allowed to specify the category (e.g., tingle) and were encouraged to use their own words. After choosing a descriptor in one category, the patient was asked if the other categories might apply to a component of the sensation. The descriptors were classified as the mechanical/tingle modality if they were chosen from Fig. 2: *question 4,* nonpainful: mechanical, movement, and tingle categories, or as thermal/pain modality if they were chosen from either question 4, nonpainful: temperature, or question 4, painful. Nonpainful sensations were designated by NP, and painful sensations were designated P.

At sites where pain was evoked, the intensity of pain was documented using a visual analog scale (VAS) anchored by the statement

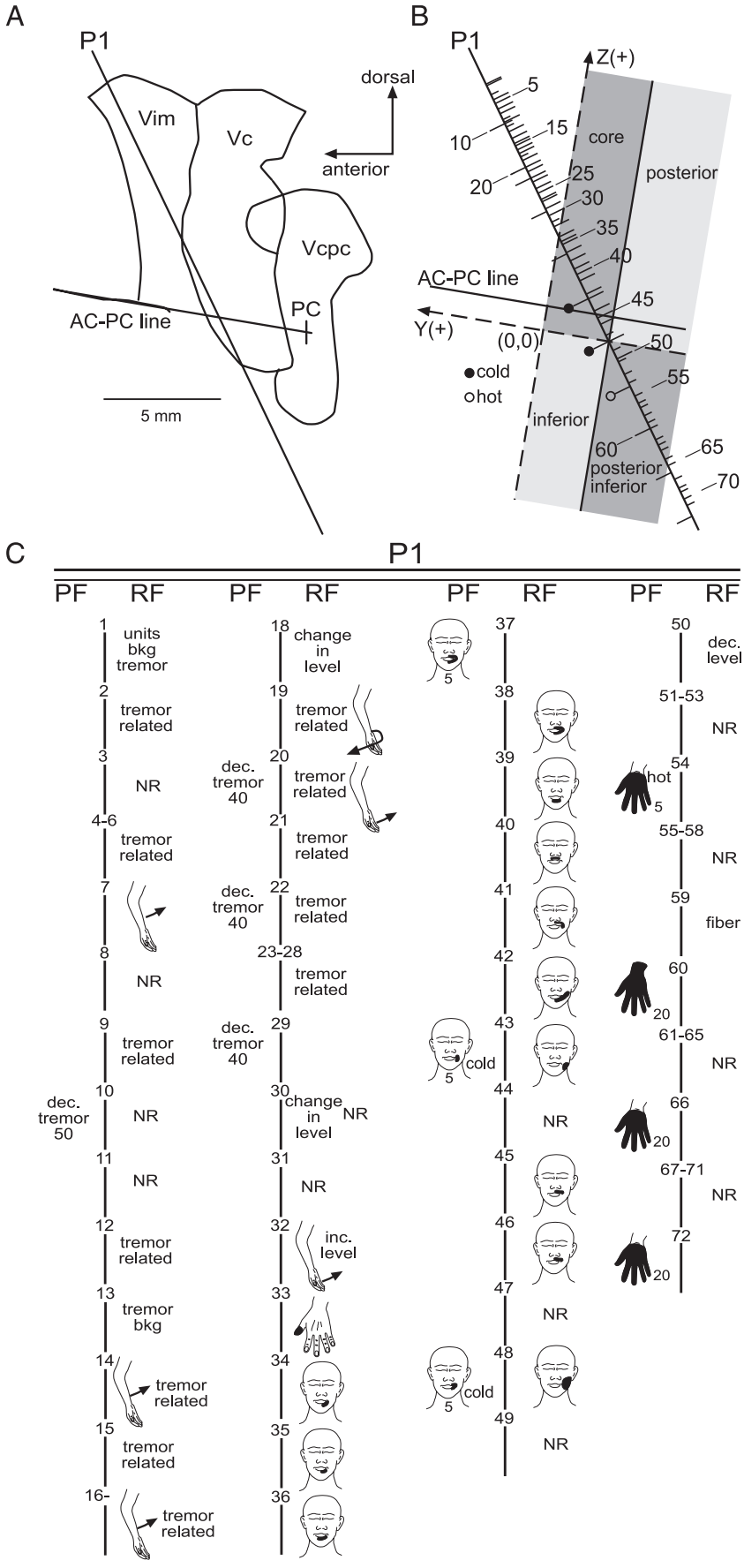

FIG. 1. Map of receptive and projected fields for trajectories in the regions of the ventral caudal nucleus (Vc) in a patient with essential tremor (180–02). *A*: positions of the trajectories relative to nuclear boundaries as predicted from the position of the anterior commissure-posterior commissure (AC-PC) line. The AC-PC line is the solid, approximately horizontal line in *A* and *B*. PC is indicated in *A*. The microelectrode trajectory is represented by the solid, oblique line. *B*: location of the neurons, microstimulation sites, along trajectory P1. The locations of microstimulation sites are indicated by tics to the left of the trajectory in *B*, while the locations of the neurons are indicated by tics to the right of the trajectory. Microstimulation sites at which a response was evoked are indicated by long tics, while those without a response are indicated by short tics. Neurons with identified activity, e.g., activity related to sensory stimulation or tremor, are indicated by long tics; those without are indicated by short tics. Sites where cool sensations were evoked are indicated by filled circles, warm by open circles. *C*: P1 shows the site number, projected field (PF, left of the line), and receptive field (RF) for that site (right). Each site where a neuron was recorded, or microstimulation was carried out, or both, is indicated by the same number in *B* and *C*. The threshold (in μA) is indicated below the PF diagram.

Which words describe the sensation that you feel?

1. Totally Natural/Almost Natural/Possibly Natural /Rather Unnatural/Totally Unnatural
2. Clearly on the skin surface/Definitely below the skin surface/Both
3. Non-painful/Painful
4. Quality of Sensation

Non-painful (NP)
- Mechanical
  - Touch
  - Pressure
  - Sharp
- Movement
  - Vibration
  - Movement through the body or across the skin
- Temperature
  - Warm
  - Cool
- Tingle
  - Electric current
  - Tickle
  - Itch

Painful (P)
- Mechanical
  - Drilling
  - Stabbing
  - Squeeze
  - Tugging
  - Tearing
  - Dull
  - Splitting
- Temperature
  - Hot
  - Burn
  - Cold
- Movement
  - Spreaad
  - Flash
  - Flicker
  - Throb
- Tingle
  - Itch
  - Electric
- Emotion
  - Frightful
  - Nauseating
  - Cruel
  - Suffocating
  - Fatiguing

FIG. 2. Questionnaire employed to describe the sensation evoked by threshold microstimulation as described in *Microstimulation protocol.*

that −10 is no sensation, 0 is the most intense sensation that is nonpainful, and 10 is the most intense pain imaginable. At sites where stimulation did not evoke pain, the following statement was used as an anchor of the scale −10 is no sensation, 0 is the most intense sensation imaginable. Microstimulation at 300 Hz was repeated to determine the projected field and to complete the questionnaire (see *Microstimulation protocol*).

This psychophysical protocol was followed at each stimulation site, and data were reported for all sites, including those where no sensation was evoked. To confirm that responses were reliable, the patient was asked to identify the onset and termination of the stimulus for both actual and sham trials of microstimulation, i.e., verbal cue without microstimulation. This protocol has been validated (Lenz et al. 1993) and used in multiple studies of sensations evoked by thalamic microstimulation (Lenz et al. 1995a, 1998, 2004).

The current level of 300-Hz current threshold was applied at stimulus trains arranged in a multiple ascending staircase protocol. This type of protocol is commonly used for psychophysical studies of thermal and experimental pain sensations (Gracely et al. 1988; Lenz et al. 2004; Yarnitsky and Sprecher 1994). Each stimulation train or step consisted of one of five different numbers of pulses (4, 7, 20, 50, 100—horizontal axes in Fig. 3), and one of 5 different frequencies of stimulation (10, 20, 38, 100, 200 Hz—vertical axes in Fig. 3). This staircase consisted of 24 stimulation trains because the step for 100 pulses—10Hz was excluded due to the duration of the train. The order of presentation of steps was as follows: four pulses, 10 Hz; four pulses, 20 Hz; . . . four pulses, 200 Hz; 7 pulses, 10 Hz; 7 pulses, 20 Hz, etc. This protocol resulted in a factorial delivery of all possible pairs of frequencies and numbers of pulses (Figs. 3 and 5). Stimulation of the steps on the staircase was repeated to define the projected field, questionnaire descriptors, and VAS score.

Statistical analyses

The threshold for evoking sensation was analyzed by the frequency and number of pulses at the location in the grid which was closest to the origin, i.e., the step with four pulses, 10 Hz (Fig. 3). The thresholds for number of pulses or frequency were determined as the lowest value of that variable in any row or column, respectively. The pulse × frequency (p×f) product was defined as the least value of the product of the number of pulses and frequency among all steps in the staircase where a sensation was evoked. If two sites were equidistant from the origin then the p×f product threshold was taken to be the lowest pulse number multiplied by the lowest frequency. These thresholds were compared between different evoked sensations by nonparametric tests as the distributions were not normally distributed. The Mann-Whitney *U* test was used for comparisons of two variables and the Kruskal-Wallis, with post hoc Dunn multiple comparison test, was used for comparisons of more than two variables.

The effect of the number of pulses and the frequency on VAS scores evoked by microstimulation in the staircase was examined with a two-way ANOVA. Post hoc testing with Tukey's honestly significant difference test (HSD) was employed for multiple comparisons. Differences in pairs of proportions were tested statistically by a Fisher test or χ^2 test, as appropriate. Differences between more than two proportions were tested by a contingency analysis with post hoc using χ^2 or Fisher using an α which was corrected for multiple comparisons (Bonferroni). All analyses were carried out using Statistica (Statsoft, Tulsa, OK); the null hypothesis was rejected for $P < 0.05$.

RESULTS

The staircase was applied at sites ($n = 110$) where threshold stimulation at 300 Hz evoked somatic sensations including thermal/pain or mechanical/tingle sensations as previously described (Lenz et al. 2004; Ohara et al. 2004). Along the staircase, there were changes in the descriptors of the microstimulation-evoked sensations at 11 sites with exclusion of changes between cool and warm sensations ($n = 3$). A change in modality occurred along the staircase at 11 of 28 pain sites (Lenz et al. 2004). These staircases were counted with both modalities for a total of 121 staircases. The number of staircases was the denominator for analyses of modality consistency, VAS and thresholds, whereas the number of sites was the denominator for analysis of place consistency.

Modality of evoked sensations: characteristics and effect of thalamic location

The proportion of thermal/pain or mechanical/tingle sensations evoked along the staircase at a site was studied as a function of location in the core, posterior superior, or posterior inferior thalamic region (Table 1). The single site in the anterior inferior quadrant (Fig. 1) was not included in the analysis. Proportions of natural versus unnatural and surface versus deep versus both categories (Fig. 2: *questions 1* and 2, Table 1) were calculated as a fraction of the total number of sites for each category because these questions were not forced choices. There were no significant differences in the location of sites where stimulation evoked the following categories: natural-unnatural, and surface versus deep versus both.

The modality of staircases was classified as follows: pain ($n = 28$), NPCool (27), NPWarm (11), and mechanical/tingle ($n = 55$). Mechanical/tingle (all NPMechanical, NPMovement, and NPTingle) tended to be evoked by microstimulation in the core more frequently than in the posterior inferior and posterior superior regions (Table 1, $P = 0.08$, 3×2 χ^2). Thermal/pain sensations were more likely to be evoked by stimulation in the two posterior regions combined than in the core (Table 1, $P = 0.009$, χ^2).

Among descriptors of microstimulation-evoked sensations significant differences ($P < 0.05$, 4×2 contingency analysis via χ^2 tests) were found both for the natural-unnatural category (Table 2) and for deep versus surface versus both categories (Table 2). Post hoc testing of the deep/surface category revealed that painful sensations were more likely to be described by a nonsurface descriptor than NPCool or NPWarm ($P = 0.002$, Fisher with Bonferroni correction, see Table 2) and mechanical/tingle sensations ($P < 0.004$, see Table 2). A similar analysis of the natural versus unnatural category by modality showed no significance ($P = 0.3$, see Table 2). Thus the location of the stimulation site and the modality of the microstimulation-evoked sensations were determinants of different characteristics of microstimulation-evoked sensations, e.g., natural/unnatural.

Reliability of evoked sensations along the staircase

We expected that at any site all steps in a staircase above the pulse–frequency threshold would evoke a response. However, at many sites (Fig. 3, *A, B*, and *D*–F), the staircase was characterized by a pattern of steps above threshold in which stimulation-evoked sensations were evoked at some (■) steps but not at other steps (▨). For example, the site illustrated in Fig. 3*E* contained gaps (▨) at three steps i.e., at 50 pulses, 20-Hz step; 50 pulses, 38-Hz step; and at 100 pulses, 20-Hz step. These were all above the pulse frequency threshold (20 pulses: 20 Hz). These gaps were defined relative to the expected right upper rectangle of the staircase, i.e., above and/or to the right of the 50-pulses, 20-Hz step in Fig. 4*E*. Missing steps were assumed to have properties intermediate between those of steps above and below, as usual, i.e., the assumption of linearity (Gracely et al. 1988).

TABLE 1. *Characteristics of sensations and thalamic region by results of 300Hz stimulation*

	Vc Thalamic Region		
	Core	Post-inferior	Post-superior
Natural	22	8	9
Unnatural	31	11	3
Surface	22	8	7
Deep	8	4	2
Both surface and deep	14	8	3
Mechanical/tingle sensations	36	11	7
Thermal/pain sensations	28	21	13

Vc, ventral caudal.

TABLE 2. *Characteristics of associated sensations and RF-PF matches as a function of sensory modality*

	Mechanical/ Tingle	Thermal/ Pain	NPWarm	NPCool	Pain
Natural	18	26	6	13	7
Unnatural	31	30	8	8	14
Surface	21	25	9	14	2
Deep	8	12	3	0	9
Both surface and deep	14	15	3	4	8

RF and PF, receptive and projected fields; NP, nonpainful.

The proportion of sites in or posterior to the core containing a gap was not significantly different between thermal/pain (36/66, 55%) and mechanical/tingle sensations (32/55, 58%; $P = 0.67$, χ^2 test). Neither was the proportion of sites with a gap significantly different ($P = 0.2$, χ^2) among mechanical/tingle (32/55, 58%), NPCool (12/27, 44%), NPWarm (9/11, 82%), and pain (15/28, 54%). Therefore by this measure the reliability of detection of a sensation was not significantly different between modalities.

Modality consistency: sensations along the staircase

If the thalamic elements of modality and place representation are discrete and nonoverlapping, then the sensations should be consistent (see INTRODUCTION) across different steps along the staircase at any site. Microstimulation-evoked cool sensations (NPCool) were usually consistent (25/27 sites), although NPCool changed to NPWarm along two staircases, at 20 pulses–20 Hz and at 20 pulses–38 Hz. NPWarm sensations were consistently NPWarm except for a change to NPCool at 20 pulses—200 Hz at one site and a change to painful heat at 20 pulses–20 Hz at another site (see following text). NPCool and NPWarm sensations were considered to be of the same modality—thermal, as usual (Mountcastle 1980; Willis and Coggeshall 1991). Thus nonpainful thermal sites had the same modality along the staircase except for one change from NPWarm to painful heat.

Along staircases where microstimulation evoked NPMechanical, NPMovement, and NPTingle sensations there were five cases where these sensations [NPTingle: $n = 4$ sites, NPMovement: $n = 1$, see (Lenz et al. 2004)] changed to pain as stimulation ascended the staircase. Overall, changes in modality along the staircase were more common for pain sensations (39%, 11/28) than for nonpainful thermal (1/38, $P < 0.001$, Fisher), or for mechanical/tingle sensations (10%, 5/55, $P < 0.002$) (Lenz et al. 2004).

This high degree of modality consistency might be due to a bias for any subject to describe all stimulation-evoked sensa-

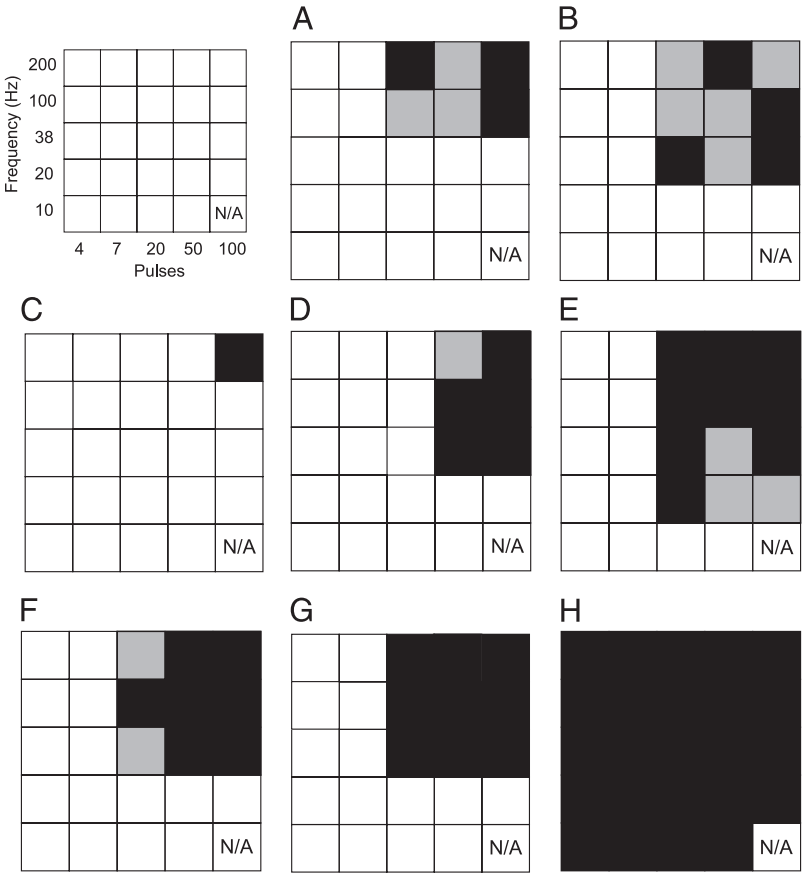

FIG. 3. Examples of gaps in microstimulation evoked sensations along ascending staircases at 8 separate sites. ■, combinations of numbers of pulses and frequencies at which sensations were evoked; ▨, gaps or steps above the pulse and frequency thresholds (see *Statistical analysis*) at which microstimulation did not evoke sensations. Microstimulation was not performed at 100 pulses/10 Hz.

tions using the same descriptors across sites, or at different steps along a staircase. To the contrary, different steps along a staircase evoked different descriptors at many pain sites (39%, see preceding text). In addition, stimulation at different sites in a patient often evoked different descriptors within a category. For example, natural and unnatural were chosen at different sites in 35% of subjects in whom those descriptors were chosen at two or more sites. In the same way, surface and deep were chosen in 38% of subjects, NPWarm and NPCool in 40%, NPMechanical and NPMovement in 60%, painful hot and painful cold in 17%, painful mechanical/movement for 33% of subjects. Therefore the modality consistency along most staircases is compatible with similarity in sensations evoked across steps within a staircase and not with a bias to choose the same descriptors either across steps within a staircase or across sites within a subject.

Place consistency: changes in projected fields along the staircase

As a test of place consistency, we measured the size of the projected field evoked by stimulation at different frequencies and numbers of pulses (Lenz et al. 1988b). The parts of the body which were considered to be different anatomic locations are given in Table 3. Using this classification, the projected field changed between steps along the staircase at a site for 5% (6/110) of sites. These sites were classified as mechanical/tingle (4), NP thermal (1), and pain (1) and were located in the core (3 sites), posterior superior (1), and posterior inferior (2). This suggests that, for most sites, the same set of neurons and axons were activated at all steps in the staircase above the pulse and frequency threshold.

Modality and place representations: incidence of more than one descriptor and more than one part of the body as a function of current threshold in the core of Vc

If there are subnuclear elements mediating modality and place specificity in Vc, then the numbers of both descriptors and parts of the body should increase with the current of microstimulation. If these elements are discrete, then the increase in the proportion of sites with more than one descriptor or a projected field with more than one part of the body (Table 3) should increase in a stepwise manner. Therefore we plotted the current threshold (300 Hz) against the cumulative proportion of sites in the core with more than one descriptor (Fig. 4, *A* and *B*) and with more than one part of the body (*E* and *F*).

The proportion of sites with more than one part of the body often rose from the lowest level and then stayed constant with increasing threshold current—a plateau, (defined below) e.g., 20–30 μA in Fig. 4, *E* and *F*. At the higher currents, the proportion of sites with more than one part of the body sometimes rose again (Fig. 4, *E* and *G*, 25 μA). To examine the properties of sites where only one modality (mechanical/tingle or thermal/pain) was evoked, we re-plotted the data for such sites and defined these sites as mechanical/tingle only (Fig. 4, *E* and *G*) and thermal/pain only sites (*F* and *H*).

The most striking aspect of Fig. 4 is the large number of plateaus in the plots of more than one part of the body (Fig. 4, *E–H*), particularly in comparison to plots of more than

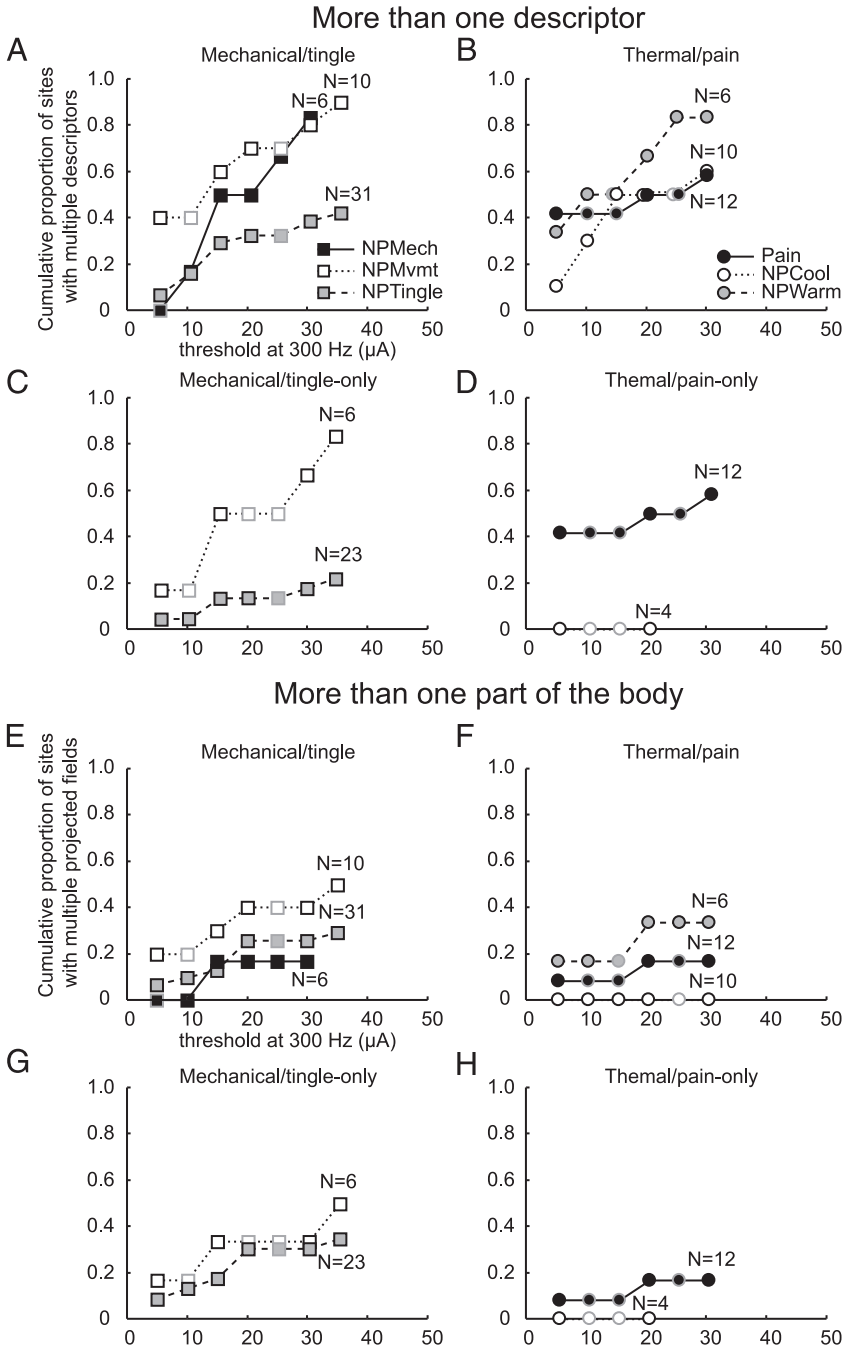

FIG. 4. Proportion of sites at which microstimulation evoked a sensation described by multiple descriptors (*A–D*) and projected fields including multiple body parts as defined in Table 4 (*E–H*). These plots show the results for mechanical/tingle (*A, C, E,* and *G*), thermal/pain evoked sensations (*B, D, F,* and *H*). The descriptors were classified into mechanical, movement, tingle, warm, cold, and pain consistent with the questionnaire (Fig. 2). The presence of a current level at which no stimulation site was found for that sensation is indicated by a symbol with a gray rather than a black perimeter, e.g., *A*: nonpainful (NP) movement. The number of sites included is indicated to the right of the plot. Plots composed of <4 sites were excluded.

one descriptor (Fig. 4, *A–D*). We defined the presence of a plateau by a constant proportion of sites with more than one descriptor (Fig. 4, *A–D*) or part of the body (*E–H*) across any three adjacent current levels, i.e., across a range of 10 μA. Three adjacent current levels were considered to constitute a plateau even if the proportion (*y* axis) was zero, e.g., cold sensations. We required the highest and lowest currents in the plateau to include at least one stimulation site as indicated by symbols with black rather than gray perimeters. The presence of a plateau was more common ($P < 0.001$, Fisher) for plots of proportions of more than one part of the body (10/10, Fig. 4, *E–H*) than for those of descriptors (1/10, *A–D*).

Figure 4 also demonstrates that the proportions of sites with more than one descriptor were higher, across all current thresholds, than those with more than one part of the body. Specifically, the proportion of sites with more than one descriptor at 30 μA was significantly higher for descriptors (0.59 $\pm$ 0.25 mean $\pm$ SD; Fig. 4, *A* and *D*) than for parts of the body (0.21 $\pm$ 0.15, *E* and *H*, $P < 0.01$, *t*-test). The proportions of sites with more than one descriptor at 5 μA (0.19 $\pm$ 0.18) tended to be larger than those with more than one part of the body (0.8 $\pm$ 0.8, $P = 0.09$, *t*-test). Therefore in comparison with the psychophysical elements of modality specificity, the elements of place specificity for both mechanical/tingle and thermal/pain sensations seem to be larger or more discrete. There were not

TABLE 3. *Sequence of medial-lateral somatotopy in the core of Vc*

RF/PF Categories	Assigned Number
Medial Vc core	
Intraoral	1
Perioral	2
Facial	3
D1	4
D2	5
D3	6
D4	7
D5	8
Multiple digits	9
Palm/hand	10
Forearm	11
whole arm	12
upper arm	13
Waist	14
Trunk	15
Leg	16
Upper leg	17
Lower leg	18
Pelvis	19
Ankle	20
Foot	21
Toes	22
Lateral Vc core	

sufficient data to carry out a similar analysis of the posterior regions.

The number of plateaus in the proportion of sites with more than one part of the body was equally high among mechanical/tingle and thermal/pain sites (Fig. 4, *E* and *F,* 6/6) and among mechanical/tingle only or thermal/pain only (Fig. 4, *A* and *B* and *E* and *F,* 4/4). To test whether these proportions are significantly different from those expected at random, we assumed that the second and third points on any plateau had a $P = 0.5$ of being greater than the preceding point. This probability was chosen based on the expectation that a reliable increase in evoked sensation will result from increased stimulation of the somatic sensory system (Dostrovsky et al. 1993; Lenz et al. 2004; Ochoa and Torebjork 1983). Therefore the probability of any plateau of three points on a cumulative proportion plot for any set of stimulation sites is estimated to be $P = 0.25$. A ratio of 4/4 or 6/6 is unlikely to occur at random based on the preceding assumptions and the assumption of a binomial distribution ($P < 0.05$). NPCool sensations in the core of Vc involved one part of the body (Fig. 4, *F* and *H,* plateaus of 4 and 6 points) and one descriptor (cool, *B* and *D,* plateaus of 3 points each) much more commonly than expected at chance ($P < 0.05$, binomial). These results and the uniformity of the plots in Fig. 4, *E–H,* suggest that elements of place-specificity are equally reliable for mechanical/tingle and thermal/pain modalities, particularly in the case of cold sensations.

An increase in the *y* value (Fig. 4, proportion of sites) from a lower to a higher level was defined as a rise if the higher level met the criteria for a plateau (see preceding text). Rises were significantly less common among plots for descriptors (Fig. 4, *A–D,* 0/10, $P < 0.002$, Fisher) than for parts of the body (7/10). In plots of proportions of parts of the body (Fig. 4, *E–H*), rises ended at plateaus having a current of 20 μA in all cases excepting one ending at 15 μA (nonpainful mechanical). These results suggest that the proposed elements of place specificity are of similar size for both mechanical/tingle and thermal/pain sensations.

Place representations: overlap of RFs and projected fields

The degree to which neurons are responsible for stimulus-evoked sensations may be estimated by correlating neuronal RFs with projected fields evoked by stimulation at the site closest to (<1 mm) the recording site for the neuron. An overlap of projected fields and RFs suggests that the neurons and axons in that area represent the same part of the body. Therefore as an additional aspect of the place representation we correlated neuronal RFs with microstimulation evoked projected fields. The medial-lateral location of each one of the cutaneous RF or projected field was assigned a number based on the established sequence of somatotopic representation in Vc from medial to lateral, i.e., intraoral to toes (Table 3) (Lenz and Byl 1999; Lenz et al. 1988b).

The overlap of the receptive and projected fields was assessed through linear regression of somatotopy of the RF with that of projected field at a site (Table 4). The NPMechanical, NPMovement, and NPTingle sensations within the mechanical/tingle modality all had significant RF-projected field correlation. Among thermal/pain sensations, RF-projected field correlation was significant only in the case of NPWarm and painful tingle sensations. This suggests that microstimulation-evoked mechanical/tingle sensations are represented in discrete thalamic elements of place specificity, which are composed of neurons and axons representing the same part of the body. NPWarm and painful tingle sites aside, such elements are less clearly defined in the case of the thermal/pain modality.

Analysis of staircase results by VAS ratings

We next examined the possibility that different patterns of stimulation evoke different intensities of sensation. The stimulation data including VAS scores for different numbers of pulses and frequencies is shown for a single site in Fig. 5 (*patient 193–02, site 28*). NPCool sensations were evoked by stimulation throughout the grid starting at 7 pulses/10 Hz and

TABLE 4. *RF-PF correlation by sensation modality and thalamic region*

Thalamic Location	No. of Sites	R^2	*P*
Core	49	0.14	0.008
Posterior Inferior	17	0.38	0.008
Posterior Superior	9	0.73	0.003
Sensation			
Natural	31	0.49	<0.001
Unnatural	36	0.28	<0.001
Surface	26	0.15	0.049
Deep	12	0.53	0.007
Both Surface/Deep	21	0.49	<0.001
NP Mech	6	0.98	<0.001
P Mech	8	0.00	0.952
NP Cool	17	0.19	0.084
NP Warm	10	0.48	0.026
NP Tingle	36	0.49	<0.001
PHotBurn	5	0.13	0.551
P Tingle	8	0.60	0.024
NP Mvmt	15	0.77	<0.001
P Mvmt	6	0.17	0.414

Correlations that achieve statistical significance are underlined.

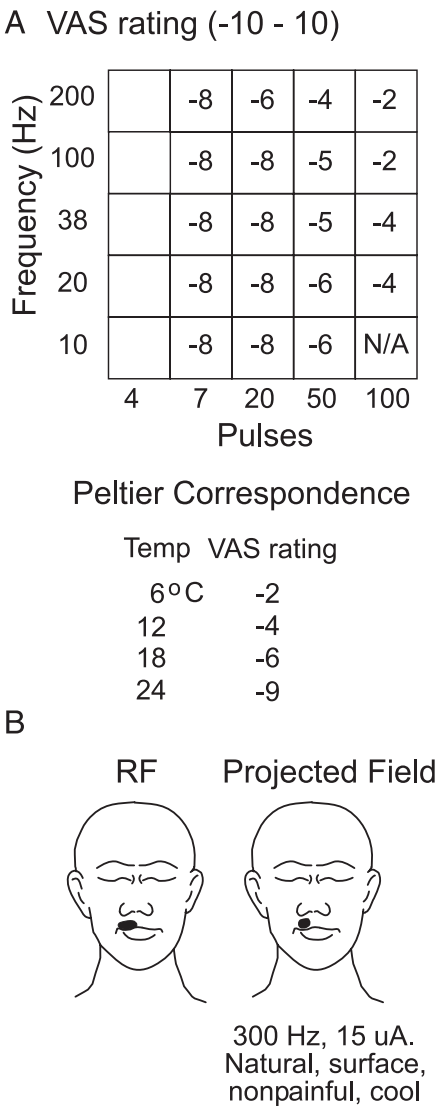

FIG. 5. Sensory ratings of thalamic and cutaneous stimuli in an individual patient. *A*: response to microstimulation at a site in the posterior inferior region (*site 28*) where microstimulation at 300 Hz and 15 μA produced a natural, cool, nonpainful, surface sensation in the area indicated on the upper lip with a VAS as indicated (see *Microstimulation protocol*). Microstimulation-evoked sensations were matched with sensations evoked by cool stimuli evoked by application of different stimuli with a Peltier device, as indicated under 'Peltier Correspondence'. *B*: map of RF and PF for this site.

increased steadily in intensity to 100 pulses/200 Hz. The highest rating of cool was −2 (scale from −10 to 10, see *Psychophysical protocols*), at the 100 pulses—100- and 200-Hz steps, corresponded to a temperature of 6°C using the Peltier stimulator applied in the projected field for this site (Fig. 5*A,* Peltier correspondence).

Ratings of NPCool sensations across all sites demonstrated a significant dependence on the numbers of pulses (a 2-way ANOVA by frequency and numbers of pulses, $F = 3.6$, df = 4, $P = 0.007$) but not on frequency ($F = 0.3$, df = 4, $P = 0.884$) or interaction ($F = 0.5$, df = 14, $P = 0.940$). Post hoc analysis showed that the sensory rating at 100 pulses (VAS = −5.9) was significantly higher than that at 7 pulses −7.3, $P = 0.009$) or at 20 pulses (−.0, $P = 0.023$). Ratings of NPWarm sensations showed no dependence on frequency ($F = 0.8$, df = 4, $P = 0.515$), the number of pulses ($F = 0.7$, df = 4, $P = 0.573$) or the interaction ($F = 0.3$, df = 16, $P = 0.996$; Fig. 6). Thus among nonpainful thermal sensations only the intensity of the NPCool sensation was dependent on the number of pulses in the stimulus train to a significant degree.

Ratings of painful heat/burn sensations showed no significant dependence on frequency ($F = 0.9$, df = 4, $P = 0.503$), the number of pulses ($F = 0.3$, df = 3, $P = 0.846$), or the interaction ($F = 0.3$, df = 4, $P = 0.884$). Painful mechanical/tingle sensations showed no significant dependence on the frequency ($F = 1.3$, df = 4, $P = 0.286$), or the number of pulses ($F = 0.5$, df = 4, $P = 0.760$), or the interaction ($F = 0.5$, df = 12, $P = 0.913$). The results at pain sites may be the result of the large number of sites where pain intensity had an all-or-none (binary) dependence on frequency, often at low pulse thresholds (Lenz et al. 2004). For example, pain characterized by mechanical, movement, or tingle descriptors (Fig. 6*E*) was commonly evoked at pulse thresholds of 4, whereas nonpainful sensations characterized by the same descriptors were never evoked at 4 pulses (Fig. 6, *A* and *B*).

Ratings of mechanical/tingle sensations were variably related to stimulus parameters. Analysis of mechanical/tingle sensations showed a significant effect of number of pulses ($F = 4.8$, df = 3, $P = 0.004$) but not frequency ($F = 1.4$, df = 4, $P = 0.25$) or interaction ($F = 0.4$, df = 12, $P = 0.976$). Post hoc analysis by number of pulses revealed that the sensory rating at 100 pulses was significantly higher than at 7 pulses ($P = 0.021$) and 20 pulses ($P = 0.022$; VAS ratings: 7 pulses, −7.7; 20 pulses, −7.2; 50 pulses, −6.5; 100 pulses, −5.6). Ratings of NPTingle sensations showed a significant dependence on the number of pulses ($F = 3.6$, df = 3, $P = 0.018$) but not frequency ($F = 1.2$, df = 4, $P = 0.312$) or interaction ($F = 0.2$, df = 12, $P = 0.996$). Post hoc analysis showed the VAS rating at 100 pulses (−6.1) was significantly higher than that at 7 pulses (−7.8; $P = 0.047$). NPMovement showed no dependence on frequency ($F = 0.4$, df = 4, $P = 0.837$), the number of pulses ($F = 0.9$, df = 3, $P = 0.477$) or interaction ($F = 0.6$, df = 11, $P = 0.776$; Fig. 6). Overall, the intensity of mechanical/tingle sensations overall, and of both NPTingle and NPCool sensations was dependent on the number of pulses. The intensity did not covary with the frequency or the interaction of pulses and frequency for any type of sensation.

Analysis of staircase thresholds by pulse, frequency, and p × f product

Thresholds along the staircase (Table 5) demonstrated that the threshold p × f product for mechanical/tingle sensations was significantly higher ($P = 0.018$, Mann-Whitney *U* test, see Table 5) than that for thermal/pain sensations. This suggests that thermal/pain sensations were evoked at lower numbers of pulses and frequencies on average. On subgroup analysis, mechanical/tingle sensations displayed a trend for difference in p × f product threshold across all modalities ($P = 0.11$, Kruskal-Wallis, see Table 5). Mechanical/tingle sensations were evoked with the highest p × f product, followed by pain, NPWarm, and NPCool (Table 5).

Mechanical/tingle sensations displayed higher frequency thresholds than did thermal/pain sensations ($P = 0.01$, Mann-Whitney *U* test, see Table 5). Frequency thresholds

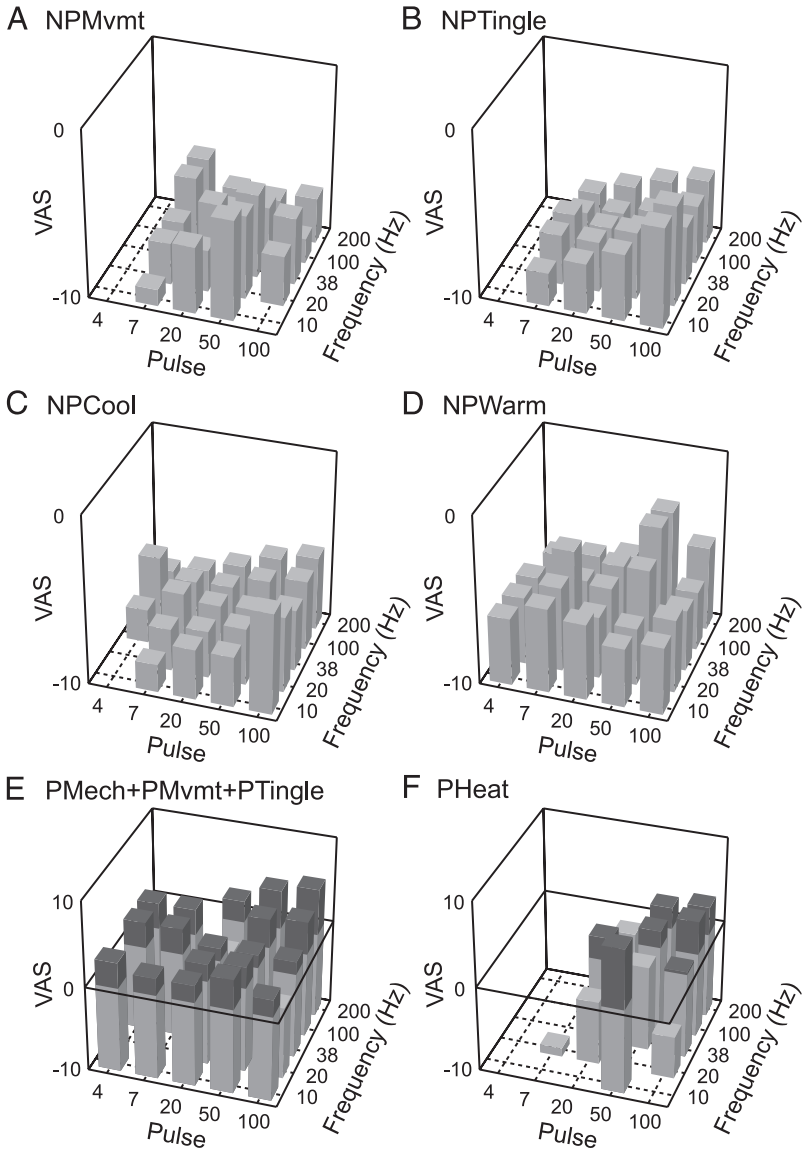

FIG. 6. Histograms of visual analog scale (VAS) ratings (−10 to 10 scale) for 300-Hz microstimulation-evoked sensation types. *A*: NPMovement; *B*: NPTingle; *C*: NPCool; *D*: NPWarm; *E*: PMech+PMvmt+Ptingle; and *F*: PHeat. Dark gray bars above the 0 level indicate VAS ratings for painful stimuli.

tended to be different between all modalities ($P = 0.09$, Kruskal-Wallis, see Table 5). Pulse threshold for mechanical/tingle sensations was significantly higher than that for thermal/pain sensations (Table 5, *2nd row,* $P < 0.04$). Pulse thresholds showed a tendency for a difference among mechanical/tingle sensations, NPWarm, NPCool, and painful sensations ($P = 0.09$, Dunn). Pulse thresholds were highest for mechanical/tingle sensations, followed by NPWarm, pain, and NPCool sensations. Thus detection a microstimulation-evoked sensation, indicated by threshold, occurred at higher numbers of pulses for mechanical/tingle than thermal/pain sensations

DISCUSSION

Based on consistency of descriptors along the staircase, modality-specificity is very commonly found for sites where microstimulation evokes NPCold, NPWarm, NPMechanical, NPMovement, or NPTingle sensations but not pain. Evidence of place specificity was found for all types of evoked sensations. Plateaus in the proportion of sites in the core with more than one descriptor as a function of current (Fig. 4) are less common than are plateaus in the proportion of sites with more than one part of the body. This suggests that the elements of modality specificity are smaller than and located within the

TABLE 5. *Number of pulses and frequency (staircase) thresholds for microstimulation-evoked sensations*

	Mechanical/Tingle	Thermal/Pain	NP Warm	NP Cool	Pain
Pulse threshold	41 ± 5	25 ± 4	31 ± 10	17 ± 3	30 ± 6
Frequency threshold, Hz	85 ± 10	51 ± 7	55 ± 17	45 ± 10	56 ± 13
Pulse-frequency product	5581 ± 1031	2840 ± 656	3622 ± 1751	1461 ± 469	3770 ± 1216

Values are means ± SE.

elements of place specificity. Both the threshold and the intensity of evoked sensations showed examples of significant correlation with the pattern of stimulation, usually with number of pulses but not frequency. Therefore present results show psychophysical evidence supporting the existence of thalamic elements of modality specificity for nonpainful sensations and of place specificity, which encode the intensity of somatic sensation.

Basis of classification of thermal/pain and mechanical/tingle sensations

It is important to consider critically the interpretation of the present results in terms of the anatomy and physiology of the primate somatic sensory pathways (Ohara and Lenz 2003). Microstimulation of mechanoreceptors can evoke sensations like those reported here for mechanical/tingle sensations (McComas et al. 1970; Ochoa and Torebjork 1983; Torebjork et al. 1984; Vallbo 1981; Vallbo et al. 1984; cf. Wall and McMahon 1985). These mechanoreceptive fibers project largely through the dorsal column (DC) and medial lemniscus to Vc, and mediate mechanical/tingle sensations as demonstrated by stimulation (Emmers and Tasker 1975; Lenz et al. 1993; North et al. 1993; Ohara et al. 2004; Tasker et al. 1982; Willis and Coggeshall 1991) and lesion studies (Nathan et al. 1986; Vierck 1998; Willis and Coggeshall 1991; cf. Wall 1970; Wall and Noordenbos 1977). These sensations may be the perceptual substrate of performance of cognitive tasks based on tactile function (Romo and Salinas 2003; Salinas et al. 2000).

Stimulation of Aδ, C, and high-threshold muscle afferent fibers evoke fast sharp, slow dull, and dull crampy pain, respectively (Torebjork et al. 1984) whereas stimulation of cool fibers evokes cool sensations (Iggo 1985). These fibers terminate on STT and spinal trigemino-thalamic neurons (Jones 1985; Willis 1985) which mediate thermal/pain sensations as demonstrated by lesion studies (Bosch 1991; Tasker 1992; Tasker et al. 1982; White and Sweet 1969) and by stimulation of the STT in the spinal cord or midbrain or within and behind Vc (Bosch 1991; Davis et al. 1999; Lenz et al. 1993; Mayer et al. 1975; Ohara and Lenz 2003; Tasker et al. 1982; White and Sweet 1969). These results suggest that thermal/pain sensations reported in this study are the result of activation of thalamic structures receiving input from the STT.

The lateral thalamic structures receiving input from the STT may be Vc and subnuclei (Fig. 1*A*) or VMpo or both. The present results (Table 1 and RESULTS) suggest that microstimulation evoked thermal/pain sensations are evoked both within and behind the core (Dostrovsky et al. 1991; Lenz et al. 1993; Ohara and Lenz 2003). Therefore these results support the view that both Vc and the region below and behind it, including VMpo (Craig et al. 1994), mediate pain and thermal sensation (Graziano and Jones 2004; Ohara and Lenz 2003; Willis et al. 2001).

Several pieces of evidence demonstrate overlap of STT and DC function. Nonpainful brushing can activate STT neurons (Willis 1985; Willis et al. 1973), and cold stimuli can activate neurons in the DC pathway (Ferrington et al. 1988). Noxious visceral stimuli can activate neurons in the postsynaptic DC pathway and lesions of this pathway can relieve visceral pain (Hirshberg et al. 1996; Nauta et al. 2000; Willis et al. 1999). Therefore our model that the input of the medial lemniscus and the STT to Vc are functionally segregated must be viewed with caution.

Thalamic elements of specificity of mechanical/tingle sensations

Microstimulation evoked sensations in projected fields which were consistent across the staircase in 94% of sites overall suggesting the presence of thalamic elements mediating place specificity. The presence of these elements is also suggested by the plateaus in the proportion of sites where more than one part of the body was evoked (Fig. 4, *E–H*). The present psychophysical evidence of elements mediating place specificity is congruent with the anatomic and physiologic evidence that cytochrome- and parvalbumin-postitive thalamic lamellae and rods are elements of place specificity for input arising from mechanoreceptors (Jones 1985; Jones et al. 1982; Lenz et al. 1988b; Mountcastle and Henneman 1952; Rausell and Jones 1991). These rods or lamellae, respectively, have a radius or mediolateral dimension of ~200–600 μm in coronal section, based on anatomic and physiologic studies (Rausell et al. 1992; Fig. 10 in Jones et al. 1982). These dimensions are congruent to those suggested by rises in the proportion of sites with more than one part of body (20 μA, Fig. 4, *E* and *G*) (Fig. 1 in Ranck 1975) and by the small proportion of sites having projected fields on more than one part of the body (Fig. 4, *E–H*) (Jones et al. 1982; Ranck 1975; Rausell and Jones 1991).

Similar evidence suggests that the thalamic elements of modality specificity are smaller than those for place specificity. Microstimulation-evoked mechanical/tingle sensations are always constant at 300 Hz and along the staircase, which demonstrates the existence of thalamic elements of modality specificity. However, the proportion of sites with more than one descriptor (Fig. 4, *A* and *C*) was commonly higher than that for one part of the body (Fig. 4, *E* and *G*), and plateaus in the descriptor plots (Fig. 4, *A* and *C*) were usually absent for NPMechanical or NPMovement sensations. The lack of plateaus in the plot of proportions of descriptors (Fig. 4, *A* and *C*) suggests that the anatomic element of modality specificity is smaller than that for place specificity, perhaps a small bundle of lemnical fibers (see Figs. 18 and 19 in Jones et al. 1982). Therefore several elements of modality specificity may be located within a rod, the probable element of place specificity for mechanical/tingle sensations.

Thalamic elements of specificity of thermal/pain sensations

The preceding review suggests that the elements of place specificity of thermal/pain sensations may be STT terminations in Vc or VP that consist of "disseminated bursts" of axonal arbors (Mehler 1962) that are located in the calbindin positive "matrix " between thalamic rods (Rausell and Jones 1991). The location of these STT terminations is coincident with that of neurons responding to noxious stimuli (Apkarian and Shi 1994). The approximate diameter of these structures is <300 μM (Fig. 8 in Rausell and Jones 1991) consistent with 20-μA current of plateaus in the proportion of more than one part of the body versus threshold for thermal/pain sensations (Fig. 4, *F* and *H*) (Ranck 1975).

The cool sensations evoked by microstimulation were highly consistent across the staircase for modality and place. Plateaus

in the relationship between proportions of sites with greater than one descriptor or part of the body were very commonly found for cool sensations (Fig. 4). The magnitude of the cool sensation varied significantly with the number of pulses in the pattern of stimulation and had the lowest pulse threshold (*Analysis of staircase results by VAS ratings*).

These results are congruent with the stimulus-response function of neurons in Vc that respond to cold stimuli (Lenz and Dougherty 1998a) and with the short bursts occurring in the spontaneous and evoked spike trains of neurons that respond to cold stimuli (Lee et al. 2005). Therefore cool sensations are mediated through discrete elements of place and modality specificity that transmit graded responses signaling the intensity of cold stimuli. Both the presence of short bursts of action potentials and the number of pulses in the stimulation train seem to be related to the microstimulation-evoked cool sensation.

Pain was often evoked at "analog" sites at which microstimulation-evoked pain commonly had both more than one descriptor at 5 μA, changes in that descriptor, and changes in intensity from the nonpainful to the painful range along the staircase. These sensations may be mediated by wide dynamic range neurons (Lee et al. 1999; Lenz et al. 2004; Price et al. 2003; Willis 1985). Pain was also evoked at "binary" sites where the descriptors and pain ratings did not change along the staircase, perhaps mediated by nociceptive specific neurons. The large number sites with more than descriptor and the lack of plateaus suggest that the modality elements of pain are small, perhaps a few thalamic neurons located within place-specific elements—the matrix between rods.

Significance of thresholds for numbers of pulses and frequencies

The present results demonstrate that thermal/pain staircase thresholds were significantly lower than for mechanical/tingle sensations. This is consistent with the response of neurons in Vc to somatic stimuli which is includes brief bursts of action potentials (low-threshold spike-bursts) (Lee et al. 2005). The burst rate is highest among neurons responding to cold stimuli, whereas microstimulation at cold sites has the lowest pulse $\times$ frequency threshold and pulse threshold. The combination of stimulus-evoked thalamic bursting (Lee et al. 2005) and sensations evoked by short bursts of microstimulation pulses (Fig. 6 and Table 5) is strong evidence that burst firing patterns encode somatic stimuli, particularly cold stimuli (Lenz and Dougherty 1998b).

The prolonged stimulus trains at threshold in the present results are consistent with earlier reports of the duration of thalamic or cortical stimulation required to evoke paresthesias (Libet et al. 1979, 1991). In these previous reports, thresholds for detection of paresthesias were determined in subjects with thalamic or cortical electrodes in place. These subjects were able to identify correctly, in a two alternative forced choice paradigm, the occurrence of stimuli that were not perceived consciously, demonstrating that the stimuli which were subthreshold for perception could be detected subconsciously (cf. Nolan and Caramazza 1982). These reports may be consistent with the present results that relatively long trains of microstimulation in Vc are required for detection of paresthesias. The present report demonstrates that as few as four pulses are often adequate for detection of microstimulation-evoked thermal/pain sensations. Therefore subconscious detection must occur over a shorter interval in the case of thermal/pain sensations (Figs. 5 and 6 C–*F*), which suggests that pain reaches consciousness more reliably than mechanical/ tingle sensations.

The short trains of microstimulation that reach consciousness at pain sites are consistent with the observations that short bursts of action potentials occur more commonly in thalamic neurons signaling pain (Lee et al. 2005) and that the response to stimulation along the staircase often evokes a constant response above threshold - an alarm (Lenz et al. 2004). An alarm is a binary, "all-or-none" response to a stimulus that is independent of the intensity of the stimulus once the threshold of the alarm is exceeded. Thalamic binary sites as an alarm, whereas analog sites serve pain transmission by encoding the quality and intensity of pain—unlike a labeled line (Craig 2003; Lenz et al. 2004; Perl 1998).

Binary processes have been reported in the cortical potentials evoked by infrequent stimuli, including infrequent painful stimuli, which produce a state of alertness and attention (Becker et al. 1993; Lenz et al. 2000; Picton and Hillyard 1988; Zaslansky et al. 1995). Binary responses also characterize blood flow signals evoked by graded, experimental, cutaneous pain in some functional imaging studies (Bornhovd et al. 2002; Coghill et al. 1999).

The binary nature of thalamic processes, pain-related imaging signals and cortical potentials signaling alertness may all reflect a common mechanism. Thalamic bursts that encode experimental pain may be a mechanism by which painful stimuli sound the alarm to produce a state of alertness and attention. Similarly, the thalamic bursts that occur in patients with chronic pain (Lenz et al. 1998c; Radhakrishnan et al. 1999; Weng et al. 2000) may contribute to the increased attention to painful stimuli that occurs in these patients (Asmundson et al. 1997; Roelofs et al. 2004).

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Analgesia and hyperalgesia from CRF receptor modulation in the central nervous system of Fischer and Lewis rats

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Abstract

This study examines the contribution of central corticotropin-releasing factor (CRF) to pain behavior. CRF is the principal modulator of the hypothalamo–pituitary–adrenal (HPA) axis, in addition to acting on many other areas of the central nervous system. We compared nociceptive thresholds (heat and mechanical) and pain behavior in response to a sustained stimulus (formalin test) between Fischer and Lewis rats that have different HPA axis activity. Intracerebroventricular (i.c.v.) administration of CRF produced dose-dependent antinociception at a lower dose in Lewis (40 ng, paw pinch 71 ± 0 g) compared to Fischer rats (200 ng, 112 ± 3 g). The antinociceptive effect of CRF was mostly preserved in adrenalectomized Fischer rats. The i.c.v. administration of the CRF receptor antagonist, astressin, had a hyperalgesic effect, suggesting that CRF is tonically active. Lewis rats required higher doses of astressin (5 ng, paw pinch 51 ± 1 g) to show nociceptive effects compared to Fischer rats (1 ng, 79 ± 1 g). Only Lewis rats vocalized during mechanical stimulus, and this behavior was prevented by diazepam or morphine but was worsened by CRF, despite its antinociceptive property. In the formalin test, CRF and astressin had the largest effect on the interphase suggesting that they act on the endogenous pain inhibitory system. CRF also increased anxiety/fear-like behaviors in the forced swim and predator odor tests. Our results establish that central CRF is a key modulator of pain behavior and indicates that CRF effects on nociception are largely independent of its mood modulating effect as well as its control of the HPA axis.

Keywords: Pain; HPA axis; Adrenalectomy; Opioid; Formalin test; Paw withdrawal

1. Introduction

Patients with chronic, diffuse, and regional pain syndromes, such as fibromyalgia syndrome, have abnormal activity of the hypothalamo–pituitary–adrenal (HPA) axis (Clauw and Chrousos, 1997; Calis et al., 2004). Because central corticotropin-releasing factor (CRF) is the main activator of the HPA axis, it is believed to be critically involved in the disease (Crofford et al., 2004; Gupta and Silman, 2004; Gur et al., 2004). The pain modulatory effect of peripheral CRF has been clearly established and is mostly dependent on the release of β-endorphin from immune cells during inflammatory processes (for review, see Schafer et al., 1997). The role of CRF in visceral pain has also been the focus of many

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studies. Central CRF appears to trigger visceral hyperalgesia via activation of parasympathetic pathways but independently of HPA axis or noradrenergic system activation (for review, see Tache et al., 2004). However, the effect of central CRF on somatic pain modulation is less clear and intracerebroventricular (i.c.v.) administration of CRF has produced conflicting results on pain behavior (see Table 2 in Lariviere and Melzack, 2000). The widespread distribution of CRF1/2 receptors in the brain offers several targets where CRF could alter pain, some of which may be independent of the HPA axis.

Fischer and Lewis rats have been useful in studying the role of the HPA axis because these inbred strains are genetically distinct (Ramos et al., 2002) and the HPA axis of Lewis rats is hyporesponsive to stressors (Sternberg et al., 1992; Dhabhar et al., 1997) compared to that of Fischer rats. Adrenocorticotropic hormone (ACTH) and corticosterone release in Lewis rats is markedly reduced in response to inflammatory or anxiogenic stimuli (Sternberg et al., 1992; Patchev et al., 1993; Dhabhar et al., 1997). Less is known about the pain behavior of these strains. Some studies have found similar nociceptive responses before and after partial sciatic nerve injury (Lovell et al., 2000) while others have reported that Fischer rats exhibit heat hyperalgesia and mechanical allodynia (Shir et al., 2001). In the formalin test, Lewis rats showed greater nociceptive responses than the SHR inbred rats (Ramos et al., 2002). As with the human studies the relationship between CRF, the HPA axis, and nociception has not been systematically studied in rats.

The goal of the present study was to determine the effect of central CRF receptor modulation on nociceptive responses. The role of the HPA axis in pain modulation by CRF was analyzed by comparing the response of Lewis, Fischer, and adrenalectomized Fischer rats to brief and sustained nociceptive stimuli and the effects of i.c.v. injection of CRF or the CRF1/2 receptor antagonist, astressin. Because CRF receptor modulation also alters anxiety and fear responses, mainly via HPA axis activation (Takahashi, 2002) and anxiety is believed to worsen pain (Wade et al., 1990; Summers et al., 1991; Fernandez and Turk, 1994; Contoreggi et al., 2004), we measured in parallel the response of both strains to stressful stimuli and the effects of centrally administered CRF and astressin.

2. Materials and methods

2.1. Animals, surgeries, and drugs

2.1.1. Animals

One hundred and ninety eight female rats (84 Lewis strain and 114 Fischer 344 strain, Charles River Laboratories, www.criver.com) were used for this study. Animals were housed on a 12 h light–dark cycle and given food and water ad libitum. Procedures for the maintenance and use of the experimental animals conformed to the regulations of UCSF Committee on Animal Research and were carried out in accordance with the guidelines of the NIH Regulations on Animal Use and Care (Publication 85-23, Revised 1996).

All rats were 3 months old at the start of the experiments. The weight of Fischer rats (180–200 g) overlapped that of Lewis rats (190–210 g). Over the period of the experiment (3 weeks), Lewis rats gained more weight ($8.3 \pm 1.5\%$) than Fischer rats ($5.6 \pm 0.5\%$) but there was no significant difference between strains ($P = 0.103$).

We did not determine the phase of the estrous cycle in Fischer and Lewis rats. The length of each estrous cycle phase is similar between both strains of rat and there is no difference in thermal nociceptive latencies across the estrous cycle in either Fischer or Lewis female rats (Terner et al., 2005). Also, it has been shown that Fischer and Lewis rats have the same levels of plasma 17β-estradiol in normal conditions or in response to lipopolysaccharide (LPS) injection (Tonelli et al., 2002). Other studies showed that female rats in different phases of the estrous cycle have the same pain behavior in the formalin test (Aloisi et al., 1996; Vincler et al., 2001) or the same HPA axis activation in response to acute stress or LPS injection (Guo et al., 1994).

2.1.2. Cannula implant for intracerebroventricular injection

Under ketamine (90 mg/kg; www.abbott.com)–xylazine (10 mg/kg Xyla-Ject; www.phoenixpharm.com) anesthesia, rats were positioned in a stereotaxic apparatus and the skull was exposed. A burr hole was drilled above the location of the left lateral ventricle at 0.9 mm posterior to bregma and 1.4 mm from the midline (coordinates from the atlas of Paxinos and Watson (1998)). A stainless steel cannula guide pedestal (www.plastics1.com) was fixed to the skull over the burr hole using four stainless steel screws (www.smallparts.com) and dental acrylic cement. The cannula guide extended into the burr hole 1 mm below the pedestal but did not touch the surface of the cortex. At least 7 days were allowed for recovery from surgery before behavioral testing was started.

2.1.3. Adrenalectomy

Twenty-four Fischer rats were subjected to bilateral adrenalectomy and 24 underwent sham surgery. Surgery was carried out under isoflurane anesthesia. A 2.5 cm, transverse, ventral incision was made to access the peritoneal cavity. The adrenal glands were then located and completely removed. Each rat received a single corticosterone pellet (35%) implanted subcutaneously at the time of the surgery. Adrenalectomized rats with corticosterone pellet were given 0.5% NaCl to drink and were weighed daily. Following perfusion, the abdominal cavity of each animal was examined to ensure removal of the adrenal glands. Sham-operated animals underwent the same procedure but the adrenals were not removed and 0% corticosterone pellets were implanted.

Corticosterone pellets were made by mixing corticosterone (www.sigmaaldrich.com) and cholesterol (www.steraloids.com) then gently heating until the mixture melted and 100 μl was poured into corticosterone pellet molds (www.tedpella.com). Each pellet contained 35 mg corticosterone and 75 mg cholesterol. Because corticosterone delivered through pellets

is unaffected by liquid intake, it is a more reliable means of delivery than adding corticosterone to drinking water in order to keep corticosterone levels constant. The dose of 35% corticosterone was based on studies by Akana et al. (1985), showing that corticosterone pellets ranging between 25% and 50% fulfill the requirement of the normal rat over a 14-day period in terms of basal and stress-induced ACTH secretion, thymus weight and body weight gain.

2.1.4. Blood sampling and estimation of plasma corticosterone

For baseline measurement, animals were transported to the testing room and were allowed to acclimate for 1 h in a quiet environment before blood collection. In the formalin test, the sampling was done 35 min after injection of formalin. The tip of the rats tail was cut (tail nick) and blood (about 300 μl) was collected using heparinized capillary (Natelson blood collecting tubes, www.fishersci.com) over a period of 2 min by a gentle rostro-caudal massage of the tail. Blood was then centrifuged at 10,000 rpm for 20 min at 4 °C. The supernatant (plasma fraction) was aliquoted and stored at −20 °C. Plasma corticosterone level was measured by enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions (Corticosterone immunoassay, cat# DE3600, www.rndsystems.com).

2.1.5. Drugs

The CRF1/2 agonist, h/rCRF, and the non-selective antagonist astressin (www.tocris.com) were diluted in sterile saline (0.9% NaCl) and administered i.c.v. in awake animals (as described below). Morphine sulfate, an opioid receptor agonist, and naltrexone, a non-selective opioid receptor antagonist (www.sigmaaldrich.com), were dissolved in saline and a dose of 4 and 1 mg/kg, respectively, was injected intraperitoneally (i.p.). The benzodiazepine receptor agonist Diazepam (Valium, www.abbott.com) was injected i.p. at a dose of 1 or 2 mg/kg. The benzodiazepine receptor antagonist Flumazenil (www.tocris.com) was given i.p. at a dose of 10 mg/kg.

2.1.6. Intracerebroventricular injections

Rats were gently restrained in a transparent, cone-shaped plastic bag with a tube attached to the tip of the cone delivering oxygen at a rate of 4 L/min. The cone had an opening so that the guide cannula was accessible. A 33-gauge beveled stainless steel cannula (www.plastics1.com) was inserted through the guide cannula (positioned over the lateral cerebral ventricle as described above) to 3.5 mm below the cortical surface. The injection cannula was connected to a 10 μl syringe attached to a microinjection pump set to deliver 2.6 μl of drug over a 2-min period.

To reduce stress, rats were acclimatized to the procedure for at least 5 days, until they entered the bag without handling. Trained rats did not show signs of discomfort during the i.c.v. injection of the drug.

2.1.7. Induction of inflammation and paw measurements

Fifty microliters of complete Freund's adjuvant (CFA; 200 μg of inactivated *Mycobacterium tuberculosis* in 170 μl of paraffin oil and 30 μl of mannide monooleate, www.sigmaaldrich.com) was injected subcutaneously in the dorsal aspect of the left hindpaw using a 30-gauge beveled needle. The hindpaw thickness was measured every 7 days up to 28 days after CFA injection using a precision dial caliper (Scienceware, www.bel-art.com). Measurements were made in the middle third of the hindpaw.

2.2. Behavioral testing

Experiments are described in Table 1. All animals were first implanted with a guide cannula. Seven days after surgery, all rats were tested every other day for mechanical and heat paw withdrawal for a minimum of five sessions (days 1, 3, 5, 7, and 9) until stable thresholds were reached. In Experiment 1, different doses of h/rCRF or astressin were given i.c.v. starting on day 11, and the nociceptive threshold (paw pinch and heat) as well as stress behaviors (predator odor and forced swim) were tested. The formalin test was given on the final day. To minimize the number of animals, each rat received up to three i.c.v. injections given on different days. Any one animal received saline or one of the drugs and no animals received both types of drugs. When an animal received different doses of the same drug, the lowest dose was given first. A minimum of 4 days was allowed between injections during which time mechanical and heat paw withdrawal testing was done to re-establish baseline values.

In Experiment 2, Fischer rats only were used. After cannula implantation and mechanical and heat paw withdrawal testing, half the rats were adrenalectomized and implanted with 35% corticosterone pellet on day 10. The other half was sham adrenalectomized. Seven days after the removal of the adrenal glands, animals were tested once again for pain behavior (paw pinch and heat) and then randomly assigned to one of two sub-groups. On day 9 post-adrenalectomy, rats of the first group received i.c.v. saline or 1000 ng h/rCRF and were tested for withdrawal threshold after mechanical and heat stimuli. Rats of the second group were injected with i.c.v. saline or 1000 ng h/rCRF followed by the forced swim test. On day 13 post-adrenalectomy, all rats underwent a formalin test.

In Experiment 3, rats were given either saline or 1 mg/kg naltrexone i.p. on day 1 and day 9 and underwent mechanical and heat paw withdrawal testing on each day.

In Experiment 4 (Lewis rats only), after cannula implantation and testing of response to paw pinch, the effect of 1 or 2 mg/kg diazepam (i.p.) either alone or after 10 mg/kg flumazenil (i.p.) on vocalization and withdrawal to mechanical stimulus was studied on day 11.

In Experiment 5, following cannula implantation and nociceptive testing, CFA was injected into the left hindpaw of rats on day 10. The size of both hindpaws was measured every 7 days until day 28 post-CFA injection. Rats were tested for withdrawal threshold after mechanical and heat stimuli 22 days after CFA injection and on the cold plate 24 days after CFA injection.

For all experiments, a treatment blind observer conducted behavioral testing between 10:00 a.m. and 2:00 p.m. On each testing day, rats were brought into the behavior room at least 30 min prior to the test session in order to habituate them to the environment. All behavior testing started 20 min after the end of the i.c.v. or i.p. injection of drugs.

2.2.1. Paw pinch

A Basile Algesimeter (www.ugobasile.com) was used to measure mechanical hyperalgesia (Randall and Selitto, 1957). The experimenter gently restrained the rat in one hand for

Table 1
Summary of experiments

Experiment 1. Pain and stress modulation by centrally administered h/rCRF or astressin (30 Fischer and 30 Lewis rats)						
Day −7	Day 1, 3, 5, 7, 9	Day 11	Day 13	Day 15	Day 17	Day 19
Cannula implant	Paw pinch + heat	Saline, h/rCRF or astressin (i.c.v.) paw pinch + heat or predator odor test	Paw pinch + heat	Saline, h/rCRF or astressin (i.c.v.) paw pinch + heat or forced swim test	Paw pinch + heat	Saline, h/rCRF or astressin (i.c.v.) formalin test
Experiment 2. Effect of adrenalectomy on CRF-modulated pain and stress behaviors (48 Fischer rats)						
			Post-adrenalectomy			
Day −7	Day 1, 3, 5, 7, 9	Day 10	Day 7	Day 9	Day 11	Day 13
Cannula implant	Paw pinch + heat	Adrenalectomy + corticosterone pellet or sham surgery	Paw pinch + heat	Saline or h/rCRF (i.c.v.) paw pinch + heat or forced swim test	Paw pinch + heat	Saline (i.c.v.) formalin test
Experiment 3. Effect of morphine or naltrexone on nociceptive thresholds (12 Fischer and 12 Lewis rats)						
Day −7	Day 1	Day 3, 5, 7	Day 9			
Cannula implant	Saline, morphine or naltrexone (i.p.) paw pinch + heat	Paw pinch + heat	Saline, morphine or naltrexone (i.p.) paw pinch + heat			
Experiment 4. Modulation of pain and distress behaviors by diazepam or morphine (i.p.) or CRF (i.c.v.) (18 Lewis rats)						
Day −7	Day 1, 3, 5, 7	Day 9	Day 11			
Cannula implant	Paw pinch + heat	Paw pinch + distress (vocalization)	Saline, diazepam ± flumazenil or morphine (i.p.) saline or h/rCRF (i.c.v.) paw pinch + distress			
Experiment 5. Effect of CFA-induced inflammation on pain behavior (24 Fischer and 24 Lewis rats)						
			Post-CFA injection			
Day −7	Day 1, 3, 5, 7, 9	Day 10	Day 7, 14, 21	Day 22	Day 24	Day 28
Cannula implant	Paw pinch + heat	CFA injection in left hindpaw (s.c.)	Paw measurement	Paw pinch + heat	Cold plate	Paw measurement

testing on the paw pinch apparatus. Nociceptive responses were collected every other day over 2 weeks (minimum of five sessions) with each testing session lasting 20 min (four measures for each paw, 5 min between each measure). No differences were observed between right and left paws and the results are presented as the average of both paw withdrawal thresholds with the exception of the CFA experiment (Fig. 6).

2.2.2. Radiant heat (Hargreaves test)

We used a commercial heat paw withdrawal device (''Plantar Analgesia Instrument'', www.ugobasile.com). The animals were placed in a Plexiglas® testing chamber (17 × 22 cm) with a floor maintained at 27–29 °C. A heat stimulus was delivered by placing a 0.5 cm diameter radiant heat source alternately under the plantar surface of the left and right hindpaws, the first paw being randomly selected to avoid anticipation by the animal. The latency to paw withdrawal was recorded. A cut-off time of 20 s was used based on preliminary experiments showing that no injury is produced within this time. Similar to paw pinch testing, four trials were performed for each paw at each session and the latency of withdrawal from all measures averaged. Heat paw withdrawal testing was carried out immediately following paw pinch testing.

2.2.3. Cold plate testing

A cold plate apparatus was used to test the response of unrestrained rats to low temperature stimulus of the plantar aspect of the paws. Rats were placed on the plate cooled to 4 °C for 5 min and each brisk lift of the hindpaw off the plate was counted. Counting of paw lifts started after 60 s and lasted 4 min (Jasmin et al., 1998). The cold plate is the most sensitive test of inflammation-induced hyperalgesia.

2.2.4. Vocalization

Vocalization was recorded using two separate tape recorders during paw pinch testing. One was connected to a microphone to record audible frequencies and the other to a Mini-3 BAT Detector (www.Noldus.com) to record 22 Hz ultrasonic vocalizations. The testing was done in a room without extraneous noise sources. The recorders were switched on at the beginning of the testing and remained on the entire session. The output of the recorders was fed via direct connection to a soundcard of a PC and the recordings were analyzed using Audacity software and the number of events recorded. Rats were assigned to the vocalization group if they vocalized during the testing of either the left or the right paw.

2.2.5. Formalin test

On the day prior to formalin test, the animals were acclimated for 1 h to the testing chambers (44 × 24 × 24 cm) that were suspended above a mirror positioned to view the plantar aspect of the rat hindpaws. On the testing day, 50 μl of 2% formalin solution in PBS (final pH 7.2) was injected subcutaneously with a 30-gauge hypodermic needle into the medial third of the plantar aspect of the left hindpaw between the second and third toe. The animal was then immediately placed into the testing chamber and continuously observed for 32 min, during which time the nociceptive pain was assessed according to a standard scoring method (Dubuisson and Dennis, 1977). Data were collected using a computer program, which automatically calculates average weighted pain scores in successive 4 min bins. The significance of the numerical scores is: 0: normal; gait and full weight bearing on the injured paw; 1: the injured paw rests lightly on the ground and toes are not splayed; 2: the injured paw is lifted completely off the floor; 3: the injured paw is licked, shaken or bitten. Thirty-five minutes following the formalin injection, tail blood was obtained for later measurement of corticosterone. One hour after formalin injection, each rat was deeply anesthetized with 100 mg/kg of pentobarbital (i.p.) and then perfused transcardially with an aldehyde fixative. The brain and spinal cord were then collected.

2.2.6. Predator odor (fox urine) stress test

The testing chamber was a standard rat cage (44 × 24 × 24 cm) and at one end a red fox urine-soaked (www.bugspray.com) cotton swab was suspended from the lid 2 cm above the bedding. The rat was placed in the cage at the end opposite to the cotton swab and was videotaped for 5 min. The following behavior was quantified: (1) time spent before burrowing or biting the lure, (2) time spent burrowing and biting, (3) number of times the rat sniffs the lure leading to immediate burrowing, (4), number of times the rat sniffs the lure without immediate burrowing, and (5) number of rearing. The number of sniffing events leading to burrowing is represented as a percentage of the total number of sniffing events. This test was done only once for any individual animal. This is considered a test of fear-like behavior.

2.2.7. Forced swim test

We followed a protocol modified from Porsolt et al. (1978). Rats were placed in a Plexiglas cylinder 20 cm diameter and 60 cm high. The cylinder was filled with 45 cm of 23–25 °C water. The water was replaced between animals. Testing was done in a quiet room. Individual animals were placed in the water and their activity was videotaped for 10 min. The animal was then removed and dried with a warm towel. The following four parameters were quantified during the last 5 min: (1) time spent immobile at the surface of water, (2) time spent swimming, (3) time spent trying to climb up the cylinder (thrashing), and (4) time spent immobile but sinking, i.e., the head is completely submerged in water. This latter behavior was not associated with any signs of distress. This test was done only once for any individual animal. This is considered a test of anxiety-like behavior.

2.3. Tissue processing

2.3.1. Histology

The formalin-perfused brains and lumbar spinal cords were post-fixed in 10% formalin for 5 h then placed in 30% sucrose in PBS (pH 7.4) for 48 h and were marked on the right side. Fifty micrometer thick transverse sections from brains of rats injected i.c.v. with saline, h/rCRF or astressin were cut on a freezing microtome at the level of the injection site. Ventricular localization of the cannula tract was verified by staining with cresyl violet. Minimal damage was caused by insertion of the cannulae as shown by a representative section (Fig. 1). For animals subjected to the formalin test, 50 μm transverse sections from the lumbar spinal cord were cut on a freezing microtome. Fos immunostaining was carried out on the L4–L5 segment where the central branches of the sensory axons from the hindpaw terminate (Takahashi et al., 2003).

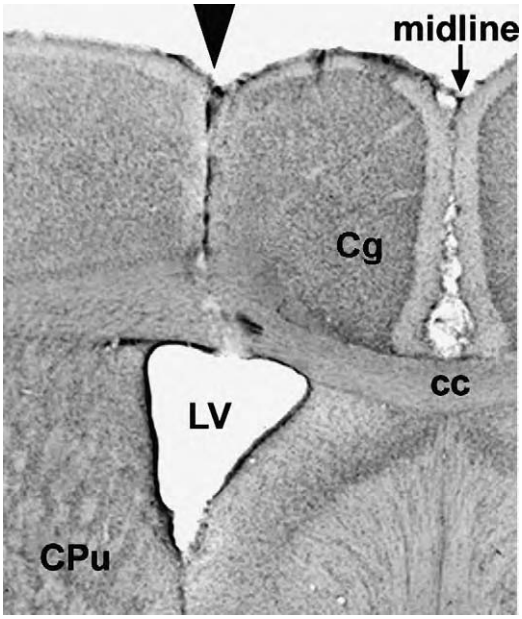


Fig. 1. Injection site of i.c.v. cannula. Nissl stained representative transverse section showing the cannula tract penetrating the cortex (arrowhead) and entering the lateral ventricle (LV). (cc) corpus callosum; (Cg) cingulate cortex; (CPu) caudate putamen.

2.3.2. Immunohistochemistry

The expression of Fos protein was used as a marker of neuronal activity (Jasmin et al., 1994). To characterize displaced cells in the spinal dorsal horn of Lewis rats, we used a number of markers: substance P and calcitonin gene-related protein (CGRP) for laminae I–II (Hokfelt et al., 1975), neurokinin-1 (NK1) receptor for lamina I (Brown et al., 1995; Littlewood et al., 1995), and mu (μ)-opioid receptor for lamina II (Arvidsson et al., 1995).

Floating sections were blocked in 5% normal goat serum (NGS) and 0.3% Triton X-100 (www.sigmaaldrich.com) in PBS for 1 h. The sections were then incubated in the primary antiserum, Fos (1:100,000, Dr. Dennis Slamon, UCLA), neuronal-nuclear protein (NeuN; 1:10,000; www.chemicon.com), substance P (1:8,000; Eugene Tech International), CGRP (1:10,000; Peninsula Labs), NK1 (1:10,000; Steve Vigna, Duke University) or μ-opioid receptor (1:4,000; Robert Elde, University of Minnesota) in 5% NGS, 0.3% Triton in PBS for 24 h, then in the species appropriate secondary antiserum (www.vectorlabs.com), diluted 1:400 in 0.3% Triton/PBS for 1 h. With the exception of Fos immunostaining, a CY3-tagged secondary antibody was used. Sections were then washed, mounted on slides, and coverslipped with Vectashield (www.vectorlabs.com) for fluorescence analysis. For Fos, a biotinylated secondary was used and then the sections were washed and incubated for 1 h in ABC Elite (# PK 6100, www.vectorlabs.com) solution diluted in 0.3% Triton/PBS. Amplification was carried out by placing sections in biotinylated tyramide for 10 min followed by incubation for 1 h in ABC Elite solution. To visualize the antibody–antigen complex, we used the nickel–diaminobenzidine (nickel–DAB) protocol. When light background appeared, the reaction was stopped by washing the sections in PBS. Since the nickel–DAB reaction can vary even with a standard protocol, immunohistochemistry for all rats to be compared with each other was done on the same day. Omitting the primary antiserum controlled for non-specific labeling.

2.3.3. Quantification of Fos immunolabeling

The individual who mapped, analyzed, and counted the Fos immunopositive material was blind to the strain and treatment of rats. Each section was analyzed under the microscope using bright and dark field illumination. The rostral–caudal level of the lumbar spinal cord section was determined according to the criteria of Molander et al. (Molander et al., 1984) and laminae I and II as well as laminae V and VI (neck) were delineated using dark field illumination. Fos immunopositive cells in laminae I–II and V–VI were counted in six non-adjacent sections from the L4–L5 spinal segment and averaged for each animal.

2.3.4. Statistical analysis

Analysis was done using the outcome variable in each experiment. Comparison of treatment groups was done using a two-tailed Student's *t*-test or ANOVA. When significant differences were found using a P value of less than 0.05, a post hoc comparison was made using Scheffé's F test to confirm significance. The percentage of baselines was calculated using the formula: (Paw withdrawal threshold after drug injection − baseline paw withdrawal threshold)/baseline paw withdrawal threshold × 100.

3. Results

3.1. Nociceptive thresholds

3.1.1. Fischer and Lewis rats

Fischer and Lewis rats were tested for baseline mechanical and heat paw withdrawal. As shown in Fig. 2, on the first day of testing (non-acclimated rats) the withdrawal thresholds were the same for the two strains. However, while the withdrawal values remained stable over time for Fischer rats, they became lower for Lewis rats by the second day of testing and continued to decrease until reaching a constant baseline value by the fifth testing session (acclimated rats) for both heat and mechanical stimuli (Fig. 2). To determine the contribution of opioid-dependent endogenous analgesia in pain responses, we administered the opioid receptor antagonist naltrexone (1 mg/kg, i.p.) 20 min before the first and fifth testing sessions in both strains. Compared with saline-injected animals the withdrawal thresholds of naltrexone-treated rats decreased on the first day of testing (Fischer $-15 \pm 4\%$ versus Lewis $-12 \pm 2\%$, $P = 0.503$), confirming that opioid-dependent analgesia occurred (Fig. 2). When naltrexone was given on the fifth testing session, withdrawal thresholds were lower for mechanical withdrawal (Fig. 2A) but remained unchanged in the heat withdrawal test (Fig. 2B) when compared to saline-injected animals. It has to be noted that on the fifth testing session, the effect of naltrexone was greater in Fischer rats than on day 1 (Fischer $-45 \pm 2\%$ versus

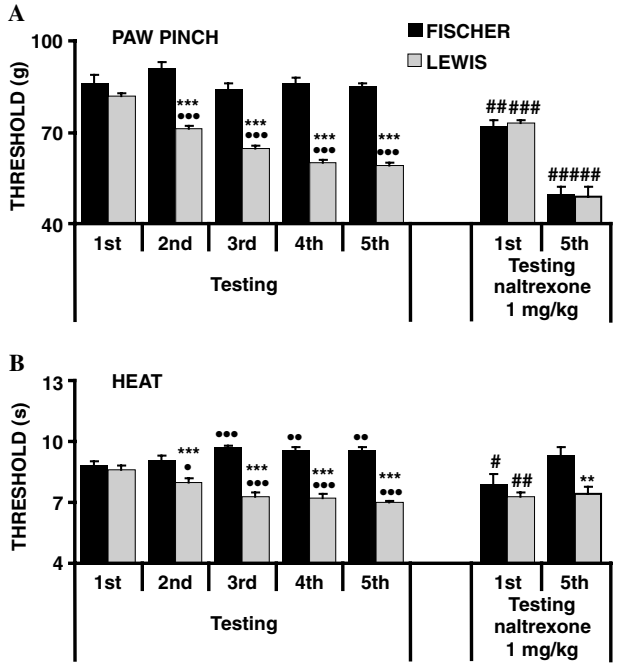


Fig. 2. Differences in withdrawal response to paw pinch (A) and to radiant heat (B) between Fischer and Lewis rats. The thresholds for Lewis rats decrease over the first five testing sessions for both tests while the threshold for Fischer rats remains stable in response to paw pinch and increases slightly after heat stimulus. Left and right paws were tested and the values averaged. Each column is the average of four measures spaced 5 min apart. The effect of naltrexone (1 mg/kg, i.p.) is given for the first and fifth testing sessions. Asterisks (*) represent the significance between Fisher and Lewis rats. $^{**}P < 0.01$, $^{***}P < 0.001$. Dots (•) represent the significance compared to the first testing. $^{\bullet}P < 0.05$, $^{\bullet\bullet}P < 0.01$, and $^{\bullet\bullet\bullet}P < 0.001$. Hash marks (#) represent the significance between saline and naltrexone-injected animals on the appropriate testing (first or fifth). $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, and $^{\#\#\#}P < 0.001$. On the first and fifth testing, thresholds from saline-injected animals were similar to those from animals without injection and are not shown.

Lewis $-18 \pm 2\%$, $P = 0.001$) and brought the mechanical withdrawal thresholds for both strains at the same level.

3.1.2. Effect of h/rCRF and astressin

We examined the effects of h/rCRF, or the non-selective CRF1/2 antagonist, astressin, delivered via a permanently implanted i.c.v. cannula. Mechanical and heat paw withdrawal testing was done in both strains with increasing doses of h/rCRF or astressin (Figs. 3A–D). The injections were carried out 2 days after animals reached baseline values, which occurred usually at the fifth testing session (see Section 2 and Table 1).

Intracerebroventricular injection of h/rCRF resulted in a dose-dependent decrease of nociception (i.e., increase of withdrawal threshold) in both strains for mechanical (Fig. 3A) and heat (Fig. 3B) stimuli. Fischer rats required a higher dose (200 ng) to obtain an antinociceptive effect when compared to Lewis rats (40 ng) in both tests. Blocking CRF receptors with astressin resulted in a dose-dependent increase of nociception (i.e., decrease of threshold) for both strains (Figs. 3C and D). Lewis rats required a higher dose of astressin (5 ng) to elicit a decrease in nociceptive thresholds. With the maximal dose of astressin used (25 ng) there was a difference between Fischer and Lewis rats in the paw pinch (Fig. 3C), but not in the heat test (Fig. 3D). The fact that blocking CRF receptors with astressin results in behavioral changes suggests there is tonic activity of CRF. It could be argued that the testing procedure itself causes an increase in CRF. We think the latter possibility less likely because the effect of the receptor antagonist (astressin) persists long after the rats were acclimated to the injection and testing procedures.

In order to evaluate the strength of the effects of centrally administered h/rCRF and astressin, the results were compared to those of morphine analgesia and naltrexone hyperalgesia, respectively (Figs. 3E and F). Because Fischer and Lewis rats had different baseline thresholds in response to paw pinch and heat stimulation, the data are represented as a percentage of baseline. Interestingly, in both Fischer and Lewis rats, the changes from baseline of CRF-induced analgesia and astressin-induced hyperalgesia were comparable to that observed with 4 mg/kg or 1 mg/kg naltrexone, respectively, only when the opioid receptor acting drugs were administered on the first day of testing (Figs. 3E and F). When injected on the last day of testing (Fig. 3E), morphine had the same effect as h/rCRF in Fischer rats for both tests. In Lewis rats, the analgesic effect of morphine was mixed giving a lower percentage from baseline after mechanical stimulus but higher after heat stimulus when compared to h/rCRF (Fig. 3E). When naltrexone was injected on the last day of testing, it produced hyperalgesia similar to astressin in Lewis rats in both tests. In Fischer rats, however, naltrexone-induced hyperalgesia was stronger after paw pinch but weaker after heat when compared to astressin (Fig. 3F).

3.1.3. Adrenalectomized Fischer rats

Because Lewis rats have a hyporeactive HPA axis and show increased pain behavior, we wished to see if removing the stress-induced increase of HPA axis activity in Fischer rats would result in a similar increase in pain behavior. Rats were tested five times for mechanical and heat paw withdrawal and then underwent bilateral adrenalectomy and corticosterone replacement. Seven days after adrenalectomy, the animals were retested and the paw withdrawal values were unchanged compared to the last day of pre-adrenalectomy testing (Figs. 4A and B). Two days later (9 days post-adrenalectomy), i.c.v. injection of 1000 ng h/rCRF elicited an increase in withdrawal thresholds for both mechanical (Fig. 4A) and heat tests (Fig. 4B) in both sham-operated and

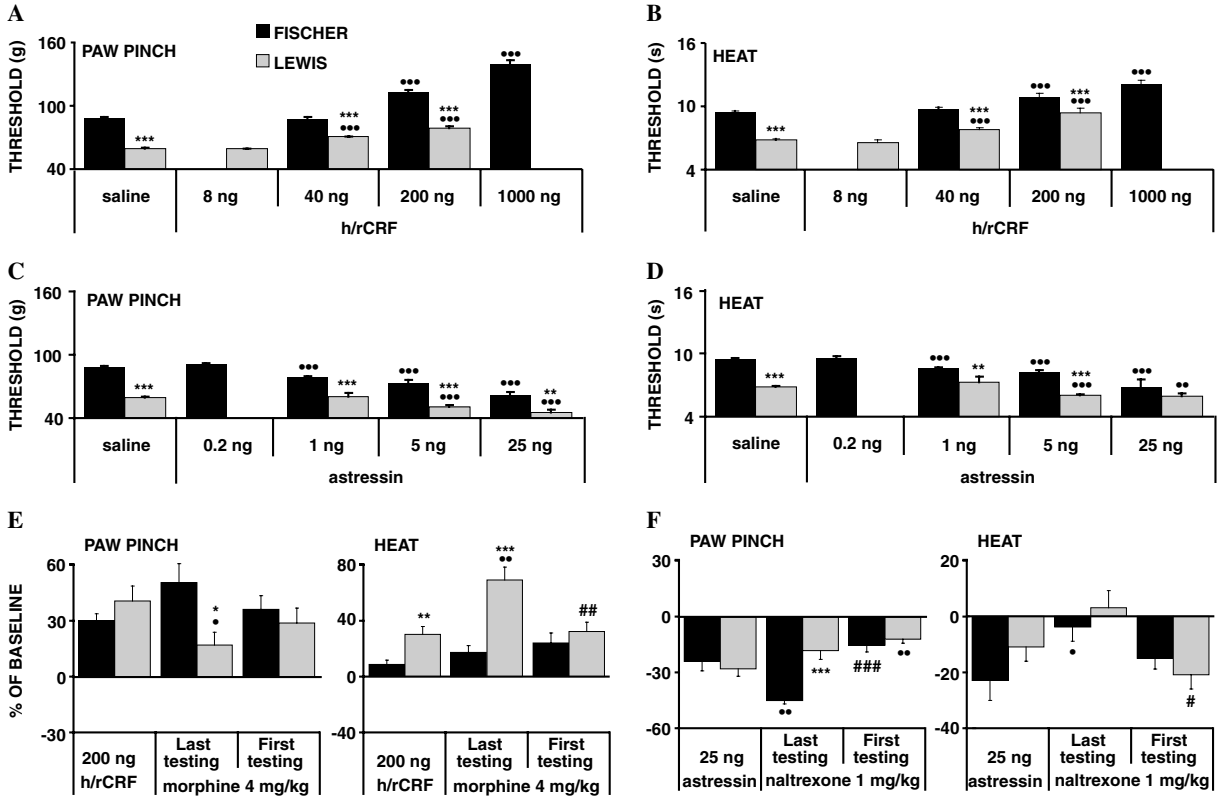


Fig. 3. Effect of h/rCRF (A and B) or astressin (C and D) on withdrawal response to paw pinch (A and C) and to radiant heat (B and D) for Fischer and Lewis rats. Intracerebroventricular injections of h/rCRF or astressin were carried out 20 min before testing. When compared to Fischer rats, Lewis rats require a lower dose of h/rCRF and a higher dose of astressin to elicit an effect in both tests. (E and F) The analgesic effect of h/rCRF (200 ng, i.c.v.) is compared to that of morphine (4 mg/kg, i.p.), while the nociceptive effect of astressin (25 ng, i.c.v.) is compared to that of naltrexone (1 mg/kg, i.p.) in both tests. Morphine or naltrexone were administered either on the first or fifth testing session. (E and F) Results are shown as percentage of baseline. In all figures, asterisks (*) represent the significance between strains. $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$. (A–D) Dots (•) represent the statistical significance of the effect of drugs (h/rCRF or astressin) compared to i.c.v. injection of saline. $^{\bullet\bullet}P < 0.01$, $^{\bullet\bullet\bullet}P < 0.001$. (E and F) Dots (•) represent the significance of the effect of i.p. morphine or naltrexone compared to i.c.v. h/rCRF or astressin, respectively. $^{\bullet}P < 0.05$, $^{\bullet\bullet}P < 0.01$. Hash marks (#) represent the significance of the effect of i.p. morphine or naltrexone between the first and fifth testing. $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, and $^{\#\#\#}P < 0.001$.

adrenalectomized Fischer rats. After adrenalectomy, the antinociceptive effect of 1000 ng h/rCRF was less in the mechanical paw withdrawal ($P < 0.01$; Fig. 4A) but similar for the heat test ($P > 0.05$; Fig. 4B), showing that the antinociceptive effect of CRF is, in part, independent of the HPA axis.

3.1.4. Distress-induced vocalization in Lewis rats

Over time, Lewis rats started vocalizing during paw pinch testing (Fig. 5A). Only audible vocalization occurred, no ultrasound was detected. While the rats did not always vocalize when their paw was pinched (five vocalizations out of 12 trials), every time they vocalized the withdrawal threshold was lower (Fig. 5B). To determine if the vocalization-associated hyperalgesia was the equivalent of the affective component of pain, we studied the effect of the anxiolytic drug diazepam on its manifestation. After diazepam injection, there was a dose-dependent decrease in the number of vocalizations. With the highest dose of diazepam (2 mg/kg), vocalization occurred during only 1 out of 12 measures (Fig. 5B). Injection of diazepam at 2 mg/kg increased the paw withdrawal threshold (78 ± 5 g) when compared with saline injection (54 ± 1 g, $P = 0.007$). The effect of 2 mg/kg diazepam was prevented by injection of 10 mg/kg of the benzodiazepine antagonist flumazenil (58 ± 3 g; versus 2 mg/kg diazepam $P = 0.018$; versus saline $P = 0.214$).

Because opioid drugs have been shown to modulate both discriminative and affective components of pain, we analyzed the effect of the opioid receptor agonist, morphine. After i.p. injection of 4 mg/kg morphine, no audible vocalization was recorded and there was an increase of the paw withdrawal threshold (72 ± 3 g, $P = 0.002$) when compared to i.p. injection of saline. Control Lewis rats injected i.p. with saline vocalized for each of the 12 measures but had similar withdrawal threshold to paw pinch (Fig. 5B) when compared to the last testing session 2 days before the injection (54 ± 4 g, $P = 0.986$).

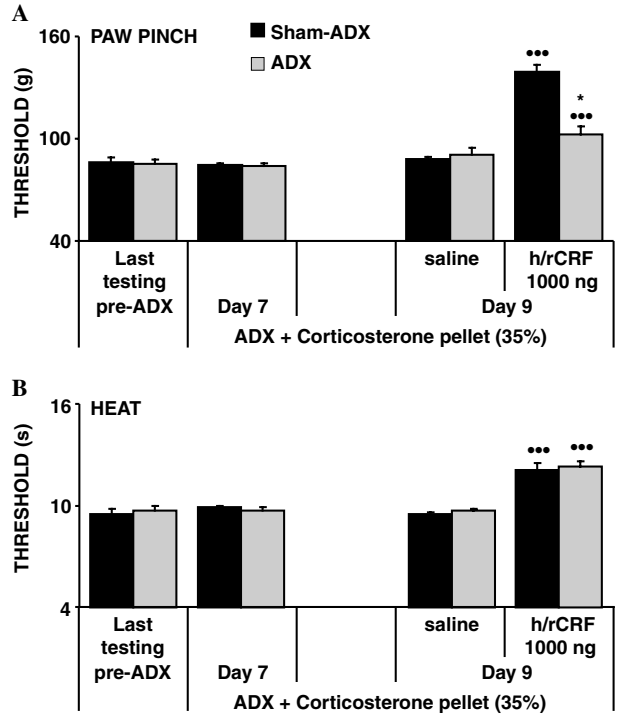


Fig. 4. Effect of h/rCRF on withdrawal response to paw pinch (A) and to radiant heat (B) in Fischer rats after adrenalectomy (ADX). Rats were tested every other day (five tests) before ADX and subcutaneous implantation of corticosterone pellets or sham surgery. When tested 7 days after surgery, animals showed no change in paw withdrawal thresholds compared to the last testing before ADX (pre-ADX). On day 9 after ADX, h/rCRF (1000 ng, i.c.v.) was given 20 min before testing. In adrenalectomized Fischer rats, h/rCRF is antinociceptive for both tests but, after paw pinch, has a lower effect than in sham-operated animals. Asterisks (*) represent the significance between adrenalectomized and sham-operated Fischer rats. $^{*}P < 0.05$. Dots (•) represent the effect of h/rCRF compared with saline. $^{\bullet\bullet\bullet}P < 0.001$.

Also, when given h/rCRF (200 ng, i.c.v.), Lewis rats vocalized for each mechanical test (Fig. 5B), despite an antinociceptive effect (i.e., increased threshold, 76 ± 3 g) when compared to i.c.v. injection of saline (59 ± 0 g, $P < 0.001$). Saline (i.c.v.) did not change the number of vocalizations or nociceptive thresholds (Fig. 5B) when compared to the previous testing session ($P = 0.141$). Finally, it should be noted that when the rats were only handled without paw pinch testing they never vocalized, so it appears that distress-associated vocalization resulted from a combination of both handling and testing.

3.2. CFA induced hindpaw inflammation

Following CFA injection in the left hindpaw, Lewis and Fischer rats developed an inflammation that persisted for the remaining 4 weeks of the experiment. While the average paw diameter throughout that period was not different between the two strains (Lewis 6.2 ± 0.5 mm; Fischer 5.9 ± 0.4 mm, $P > 0.05$), skin erosion and scaling were obvious in Lewis rats. The latter were less likely to put weight on their inflamed hindpaw and exhibited shorter withdrawal latencies to heat on the left side (Fig. 6B). Paw pinch testing of Lewis rats revealed hyperalgesia in both hindpaws, which was more pronounced on the CFA-injected side (Fig. 6A). In Fischer rats, only the inflamed paw was hyperalgesic after mechanical stimulus (Fig. 6A). On the cold plate, both Lewis and Fischer rats had a greater number of paw lifts on the inflamed side (Fig. 6C). There was no strain difference in the number of lifts for the right hindpaw.

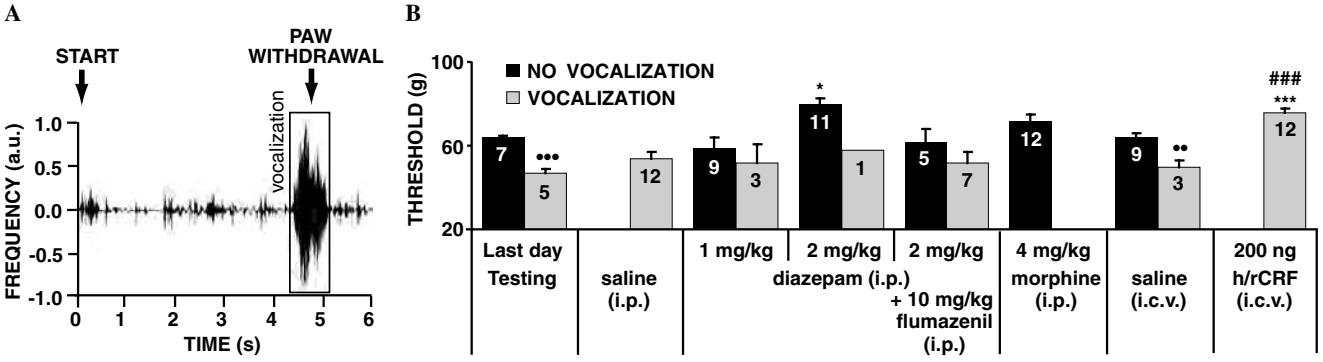


Fig. 5. Vocalization of Lewis rats during paw pinch. (A) Representative spectrum of audible vocalization recorded during paw pinch testing. The start of the mechanical stimulus and the time of paw withdrawal are indicated by arrows and the audible vocalization during withdrawal is outlined. (B) Effect of diazepam (i.p.), morphine (i.p.), and h/rCRF (i.c.v.) on vocalization and withdrawal threshold after paw pinch. In each group, three rats were each tested four times (i.e., 12 trials). The paw withdrawal measures were averaged for rats that did not vocalize (black columns) and those that vocalized (gray columns). The number in the columns indicates the number of trials resulting in no vocalization or vocalization. The withdrawal threshold is always lower in trials when vocalization occurs. Diazepam elicits a dose-dependent decrease of the number of vocalizations but only the higher dose (2 mg/kg) produces analgesia (i.e., increased threshold). The effect of diazepam on vocalization and paw withdrawal threshold is reversed by flumazenil. Injection of morphine (4 mg/kg) increases the withdrawal threshold and abolishes the vocalization. Note that i.p. injection of saline causes an increase in vocalization but does not affect the withdrawal threshold when compared to the last testing. The injection of h/rCRF (200 ng) increases the threshold but also increases the number of vocalizations. Dots (•) represent the difference in withdrawal threshold between vocalization and no vocalization groups. $^{\bullet\bullet}P < 0.01$, $^{\bullet\bullet\bullet}P < 0.001$. Asterisks (*) represent the significance compared to vocalization or no vocalization groups on the last day of testing. $^{*}P < 0.05$, $^{***}P < 0.001$. Hash marks (#) represent the significance of drug compared to i.c.v. saline. $^{\#\#\#}P < 0.001$.

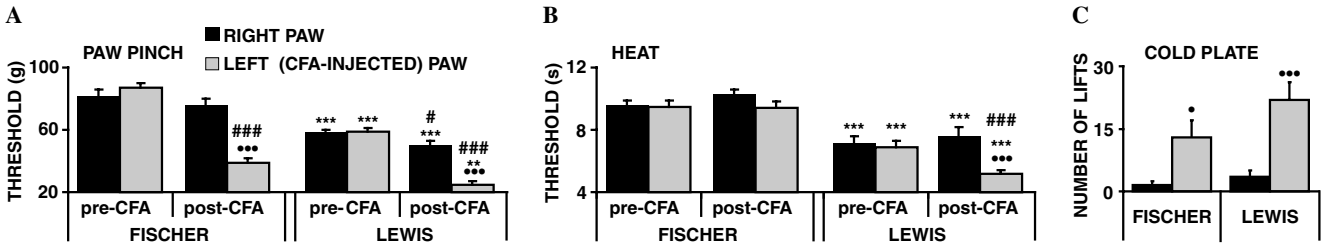


Fig. 6. Effect of CFA-induced inflammation on paw withdrawal thresholds after paw pinch (A) or heat (B) and on the number of lifts in the cold plate test (C). CFA was injected into the left hindpaw. Asterisks (*) represent the significance between Fischer and Lewis rats. $^{**}P < 0.01$, $^{***}P < 0.001$. Dots (•) represent the difference between the left (CFA) and right paws. $^{\bullet}P < 0.05$, $^{\bullet\bullet\bullet}P < 0.001$. Hash marks (#) represent the significance between pre- and post-injection of CFA. $^{\#}P < 0.05$, $^{\#\#\#}P < 0.001$.

3.3. Formalin test

3.3.1. Pain behavior

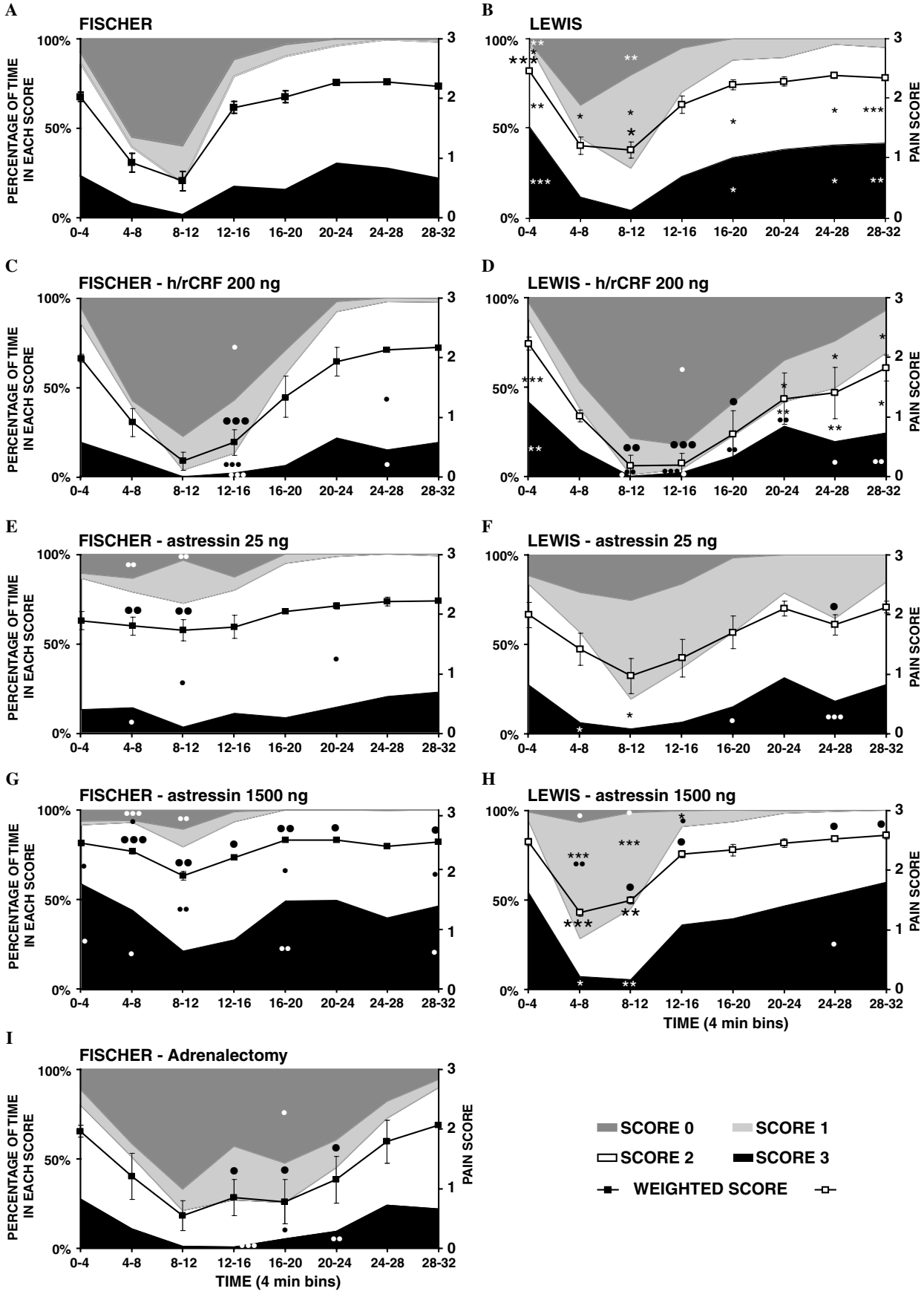
The pain behavior induced by intraplantar injection of formalin is characterized by two phases of high pain behavior separated by an interphase of reduced pain behavior (Dubuisson and Dennis, 1977). Usually, the first phase lasts for about 4 min, the interphase for about 8 min, and the second phase for at least 40 min. Compared to Fischer rats, Lewis rats had a significantly higher pain score in the first phase and interphase of the test (Figs. 7A and B). In the second phase, even though the weighted pain score was not different between the two strains, it can be seen that Lewis rats spent significantly more time in score 3 for several time points.

In the formalin test, as with the acute tests, h/rCRF (200 ng, i.c.v.) reduced the pain score in both strains (Figs. 7C and D) compared to saline-injected animals but the effect was greater in Lewis rats. After h/rCRF injection, there was no longer any difference between strains for the weighted pain score, although the time spent in score 3 was higher in Lewis rats in the first phase of the test. For both strains, the interphase was prolonged to 16 min, as the result of increased time spent in score 0 and complete loss of licking behavior (score 3). The 200 ng h/rCRF dose was chosen because it was effective in the acute tests for both strains, but it should be noted that this dose was the lowest effective dose for Fischer rats but in the upper range of the dose curve for Lewis rats (Figs. 3A and B). Thus, the effect was probably maximal for Lewis but not for Fischer rats.

When astressin (25 or 1500 ng, i.c.v.) was injected before the formalin test, the largest effect was seen in Fischer rats (Figs. 7E and G) as shown by a dramatic dose-dependent increase of the weighted pain score compared to saline-injected rats (Fig. 7A). The most striking difference was that the reduction in pain score usually seen in the interphase (4–12 min, Figs. 7E and G) was abolished, resulting from a decrease of score 0 for the two time points with 25 or 1500 ng astressin. There was a dramatic increase of licking behavior (score 3) after the 1500 ng dose of astressin (Fig. 7G). The effect of astressin in Lewis rats was not as clear (Figs. 7F and H) and compared to the saline-injected rats (Fig. 7B), there was no difference between any points on the average weighted pain score in the first phase and the interphase with 25 ng astressin. With the dose of 1500 ng astressin, only a slight increase of the weighted pain score was observed at the end of the interphase (8–16 min, Fig. 7H) and also during the second phase of the test (24–32 min, Fig. 7H). Even though there appeared to be a difference in the interphase between Fischer and Lewis rats for both doses of astressin, statistical significance was only observed with the 1500 ng dose of astressin (Figs. 7G and H).

Next, the behavior of the adrenalectomized rats was assessed in the formalin test (Fig. 7I). Adrenalectomy did not result in any difference in the weighted pain score in the first phase of the formalin test. There was,

Fig. 7. Formalin test (50 μl of 2% formalin in the plantar aspect of the left hindpaw) in Fischer (A, C, E, G, and I) and Lewis rats (B, D, F, and H) after i.c.v. injection of saline (A and B), 200 ng h/rCRF (C and D), 25 ng astressin (E and F), 1500 ng astressin (G and H), or after adrenalectomy (I, only Fischer rats). In all formalin test graphs, the percentage of time for each of the four scores (see Section 2) is presented in addition to the weighted average pain score. The percentage of time (left ordinate) in each score and the weighted average pain score (right ordinate) for each 4 min bin are shown. After i.c.v. injection of saline, Lewis rats (B) have a higher pain score in the first phase (0–4 min) and the interphase (4–12 min) of the test and spent more time in score 3 (licking behavior) during the second phase (12–32 min) when compared to Fischer rats (A). Injections of h/rCRF or astressin were carried out 20 min before the formalin injection. The 200 ng dose of h/rCRF has an antinociceptive effect in both strains, prolonging the interphase (C and D). Both doses of astressin abolish the interphase in Fischer rats (E and G) but have only a slight effect in Lewis rats (F and H). Adrenalectomized Fischer rats (I) have a lower pain score compared to sham and what appeared to be a longer interphase. Asterisks (*) represent the significance between strains. $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$. Dots (•) represent the significance of drugs compared with saline-injected animals (A and B). $^{\bullet}P < 0.05$, $^{\bullet\bullet}P < 0.01$, and $^{\bullet\bullet\bullet}P < 0.001$. Large symbols correspond to the weighted pain score and small symbols to individual scores (black or white).


A
FISCHER
B
LEWIS
C
FISCHER - h/rCRF 200 ng
D
LEWIS - h/rCRF 200 ng
E
FISCHER - astressin 25 ng
F
LEWIS - astressin 25 ng
G
FISCHER - astressin 1500 ng
H
LEWIS - astressin 1500 ng
I
FISCHER - Adrenalectomy
PERCENTAGE OF TIME IN EACH SCORE
PAIN SCORE
100%
50%
0%
0
1
2
3
0-4
4-8
8-12
12-16
16-20
20-24
24-28
28-32
TIME (4 min bins)
SCORE 0
SCORE 1
SCORE 2
SCORE 3
WEIGHTED SCORE

however, a marked decrease of the pain score in the interphase and the early part of the second phase (time points 12–24 min), as the result of an increase of score 0 and the loss of licking behavior (Fig. 7I compared with Fig. 7A).

3.3.2. Plasma corticosterone measurement

As corticosterone levels reach their maximum value approximately 35 min after the onset of a stressor (Akana et al., 1985), we chose to terminate the formalin test scoring at 32 min in order to sample blood for corticosterone measurement at 35 min. The baseline values for both strains were not different (Table 2). Thirty-five minutes after the start of the formalin test the corticosterone levels increased in both strains with the Fischer strain having the highest levels. Neither h/rCRF (200 ng, i.c.v.) nor astressin (25 ng, i.c.v.) caused any further change in corticosterone levels in the Fischer strain, while in Lewis rats both drugs led to further increase in corticosterone levels. For all conditions the corticosterone levels were lower for the Lewis than for the Fischer strain. In adrenalectomized Fischer rats, the formalin stimulus had no effect on the circulating level of corticosterone, which was entirely dependent on the fixed replacement therapy.

3.3.3. Fos immunostaining

One hour following the formalin injection, the rats were euthanized and the lumbar spinal cord processed for Fos immunostaining (Fig. 8A). The number of Fos immunopositive cells was counted in spinal laminae I/II (Fig. 8B) and V/VI (Fig. 8C) of the L4–L5 segment. Examination of the spinal cord of Lewis rats showed that the medial aspect of their dorsal horn was abnormal (Fig. 8A). Fiber bundles broke up the superficial region of the dorsal horn and there were tongues of gray matter projecting into the dorsal columns. Fos positive nuclei (Fig. 9A) were present in this region and colocalized with NeuN (Fig. 9B) showing that Fos positive displaced cells were neurons (Fig. 9C). To confirm that the disrupted region presented the immunocytochemical characteristics of the superficial dorsal horn, we examined the distribution of substance P (Fig. 9D), CGRP (Fig. 9E), μ-opioid receptor (Fig. 9F), and NK1 receptor (Fig. 9G), and these were all present. NK1 receptor immunostaining indicated that Fos positive neurons were located in lamina I of spinal dorsal horn (Fig. 9G), so when the displaced cells were Fos positive they were included in the counts. Although these displaced regions had the characteristics of normal dorsal horn, we cannot rule out the possibility that this abnormal neuronal migration in the lumbar superficial dorsal horn of Lewis rats could be responsible for some of the behavioral differences.

The analysis of laminae I/II showed that following the formalin injection there was no difference in the number of Fos immunopositive cells between saline-treated Fischer and Lewis rats (Fig. 8B). After i.c.v. h/rCRF (200 ng), there was an increase in the number of Fos cells in Fischer rats but no change in Lewis rats compared to saline-injected rats. After i.c.v. astressin (25 ng), the number of immunopositive cells was decreased in Fischer rats but again was unchanged in Lewis rats. The number of Fos labeled cells in laminae V/VI showed the same pattern of increase and decrease but reached significance compared to saline-treated animals only in Fischer rats treated with h/rCRF (Fig. 8C). In adrenalectomized Fischer rats, the number of Fos cells was the same in all laminae as sham-adrenalectomized or i.c.v. saline-treated normal Fischer rats.

3.4. Anxiety-like responses

Because CRF receptor stimulation directly affects anxiety-like behavior, we examined the possibility that the antinociceptive effects of CRF were due to a decrease in responses to other threatening conditions. Initially both strains were tested in the open field test and the elevated plus maze but there were no differences in either test (data not shown). However, there were net

Table 2
Plasma corticosterone – baseline and experimental levels

	Baseline	Formalin test after 35 min		
		Saline	h/rCRF (200 ng)	Astressin (25 ng)
Fischer	39.6 ± 12.0[h]	569.8 ± 71.3[a] (×14.4)[g]	584.2 ± 31.7[a] (×14.7)	559.5 ± 34.1[a] (×14.1)
Lewis	62.3 ± 16.3	273.1 ± 12.4[a,e] (×4.4)	458.0 ± 12.5[a,b,f] (×7.4)	432.5 ± 43.0[a,c,f] (×6.9)
Fischer ADX	79.6 ± 14.1[f]	86.6 ± 26.9[d]		

[a] $P < 0.001$ versus Baseline.
[b] $P < 0.001$; [c]$P < 0.05$ versus Saline.
[d] $P < 0.001$; [e]$P < 0.01$; [f]$P < 0.05$ versus Fischer.
[g] The value in brackets is the ratio of baseline to experimental values.
[h] Corticosterone values are in ng/ml. ADX, adrenalectomy.

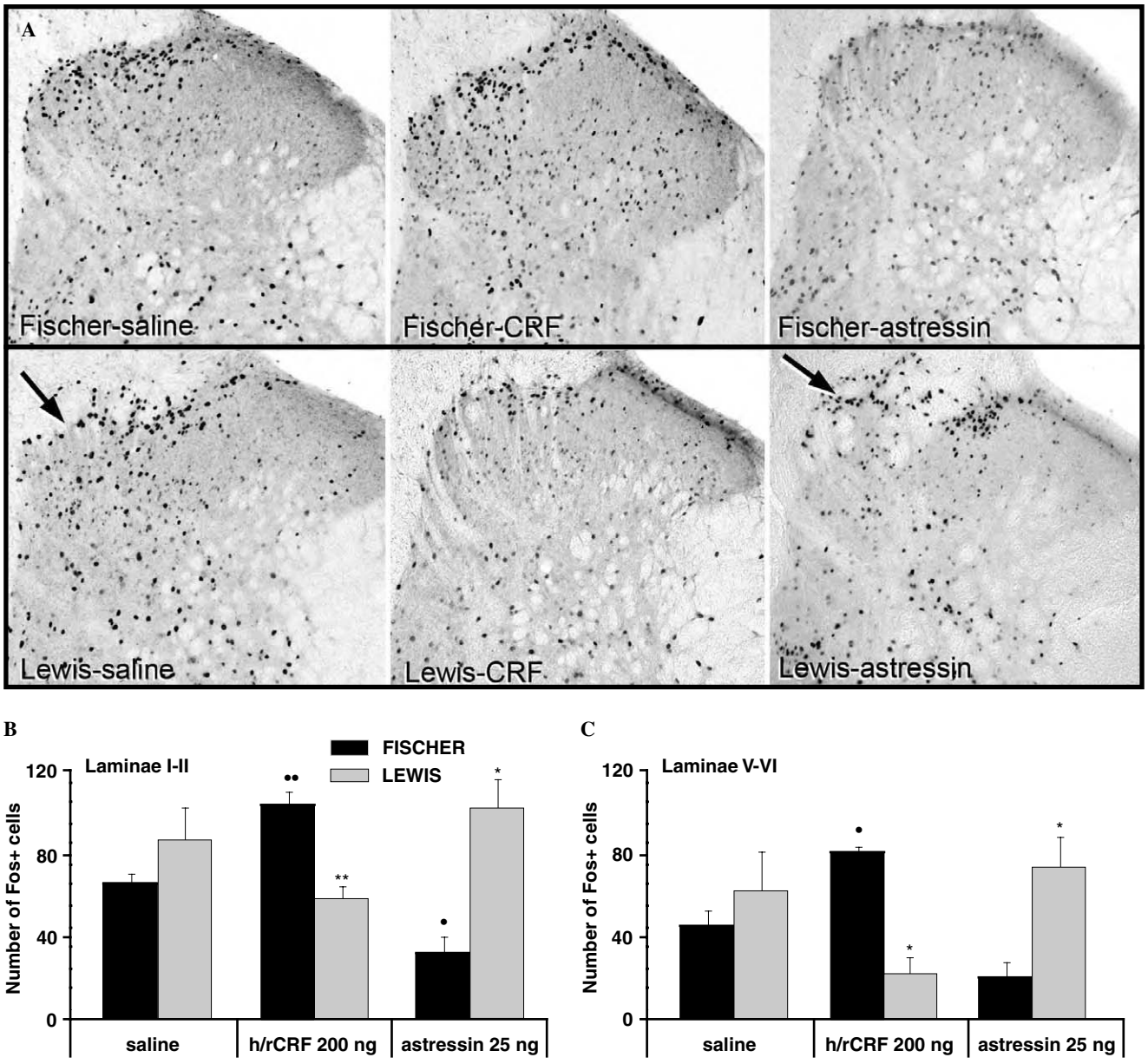


Fig. 8. Fos immunostaining of lumbar spinal cord from Fischer and Lewis rats after formalin test and i.c.v. injection of h/rCRF or astressin. (A) Animals were euthanized 1 h after the beginning of the formalin test and transverse spinal sections (L4–L5 segment) immunolabeled for Fos. Arrows indicate the projection of the dorsal horn into the dorsal columns in Lewis rats. Fos immunopositive cells were counted in laminae I–II (B) and laminae V–VI (C) for each group (four animals per group). Asterisks (*) represent the significance between Fischer and Lewis rats. $^{*}P < 0.05$, $^{**}P < 0.01$. Dots (•) represent the significance of drugs compared with saline-injected animals. $^{\bullet}P < 0.05$, $^{\bullet\bullet}P < 0.01$.

differences in the forced swim test (Fig. 10) and the predator odor test (Fig. 11).

In the swim test, Lewis rats spent more time submerged, less time swimming, and the same time thrashing compared to Fischer rats (Fig. 10). In the predator stress test, Lewis rats had a significantly longer delay time until the start of burrowing and the time spent burrowing was far less than for Fischer rats (Fig. 11). h/rCRF (200 ng, i.c.v.) in Lewis rats increased the time spent thrashing and swimming and decreased the time submerged in the forced swim test (Fig. 10A). The dose of 40 ng resulted in increased burrowing but the effect was lost at a higher dose (200 ng, Fig. 11A). h/rCRF (200 ng) in Fischer rats resulted in decreased submerged time in the forced swim test (Fig. 10A). The same dose had no effect in the predator test but a larger dose of 1000 ng resulted in increased burrowing (Fig. 11A).

Astressin (25 and 1500 ng, i.c.v., hyperalgesic doses for both strains) decreased the stress behavior in the forced swim test for both strains as measured by decreased thrashing and increased time submerged

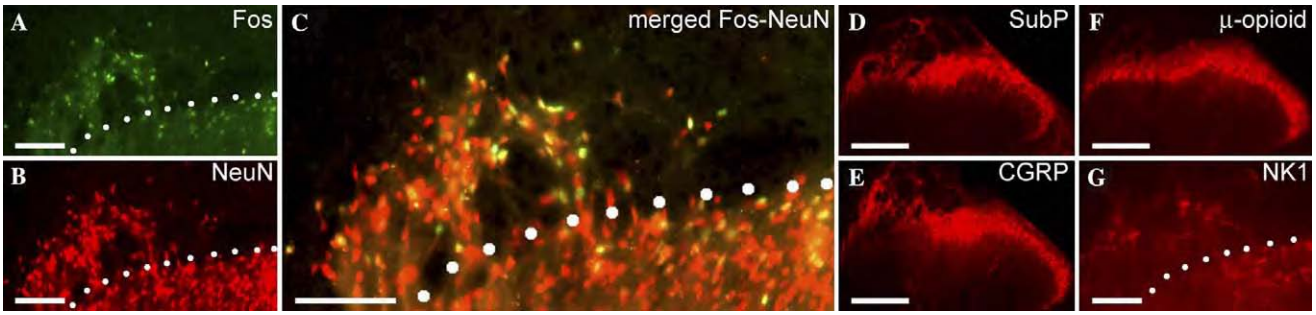


Fig. 9. Immunostaining of the dorsal horn of the spinal cord (L4–L5 segment) from Lewis rats. Double staining for Fos (A, green) and NeuN (B, red) shows that the Fos immunopositive nuclei are neurons in the region where the dorsal horn cells enter the dorsal column (C, yellow). Fibers projecting into this region are stained for substance P (SubP, D) or CGRP (E), but not μ-opioid receptor (F). Neurons immunolabeled for NK1 receptor (G) are also present in this area of the dorsal horn. Dashed lines indicate the normal limit of the superficial dorsal horn. Scale bars: A–C and G = 100 μm; D–F = 200 μm.

(Fig. 10B). Indications of decreased stress behavior were also seen in the predator odor test with decreased time spent burrowing in Fischer rats and decreased percentage of sniffing leading to burrowing in Lewis rats (Fig. 11B).

The results suggest that Lewis rats are less reactive than Fischer rats to innocuous stressful stimuli and that h/rCRF increases anxiety-like behavior in both strains while astressin had anxiolytic effects (Figs. 10 and 11).

Adrenalectomy of Fischer rats increased the time spent immobile in the forced swim test (Fig. 10A) and these animals never sank (Fig. 10A). h/rCRF (1000 ng, i.c.v.) in adrenalectomized rats also increased the stress behavior as measured by a decrease in immobility and increase in thrashing (Fig. 10A).

3.5. Motor behavior

Although CRF administration can affect motor responses, there is no evidence that it causes a motor deficit (Ohata et al., 2002; Zorrilla et al., 2002). It is unlikely that in our experimental protocol the differences in nociceptive threshold observed between the two strains were due to increased motor responsiveness in Lewis rats. Both strains withdrew at the same threshold when tested with von Frey hairs, and were not different in locomotor activity when tested on the rotarod, elevated plus maze or open field (data not shown), in agreement with previous studies comparing female Lewis and Fischer rats (Ramos et al., 1997).

4. Discussion

This study shows that activation of brain CRF receptors reduces pain behavior through central neural circuits that appear largely independent of the HPA axis. Endogenous CRF appears to tonically inhibit nociceptive responses because blocking CRF receptors is hyperalgesic. Our results also show that changing the activity of CRF receptors changes pain behavior in an opposite direction to anxiety/fear-like behavior suggesting that the two phenomena are independent. Finally, altered CRF neurotransmission might underlie strain differences in pain behavior. Whether the pain modulatory effects of CRF and astressin (Perrin et al., 1999; Ho et al., 2001) are mediated by CRF1 and/or CRF2 receptors remains to be determined. Currently, for the central nervous system the evidence favors a role of the CRF1 receptor (Bakshi et al., 2002).

4.1. The central analgesic effect of CRF is mostly independent of the HPA axis

CRF transmission has been suggested to affect pain behavior through the HPA axis from the release of corticosterone (Pavcovich and Valentino, 1997; Lariviere and Melzack, 2000; Wang et al., 2004). Our results from corticosterone measurements in the formalin test do not support this idea. In agreement with Taylor and colleagues (Taylor et al., 1998) we found that the formalin stimulus increased the levels of circulating corticosterone. However, in Lewis rats, both CRF and astressin increased circulating levels of corticosterone to the same degree (Table 2) even though their effect on pain behavior was different. Further, in Fischer rats neither CRF nor astressin alters the levels of corticosterone following the formalin stimulus although they had opposite effects on pain behavior. Moreover, adrenalectomized Fischer rats had less pain behavior despite their non-functional HPA axis, although this finding contrasts with that of another study (Taylor et al., 1998) showing no changes in the formalin test after adrenalectomy. This difference might be due to the use of Sprague–Dawley rats and the measurement of different parameters. Finally, after adrenalectomy, Fischer rats retained normal nociceptive thresholds and the antinociceptive effect of i.c.v. CRF remained for paw pinch and heat stimuli.

The HPA axis could affect pain independent of the adrenal glands by release of ACTH or β-endorphin from the pituitary (Dunn et al., 1987; Bogdanov and Yarushk-

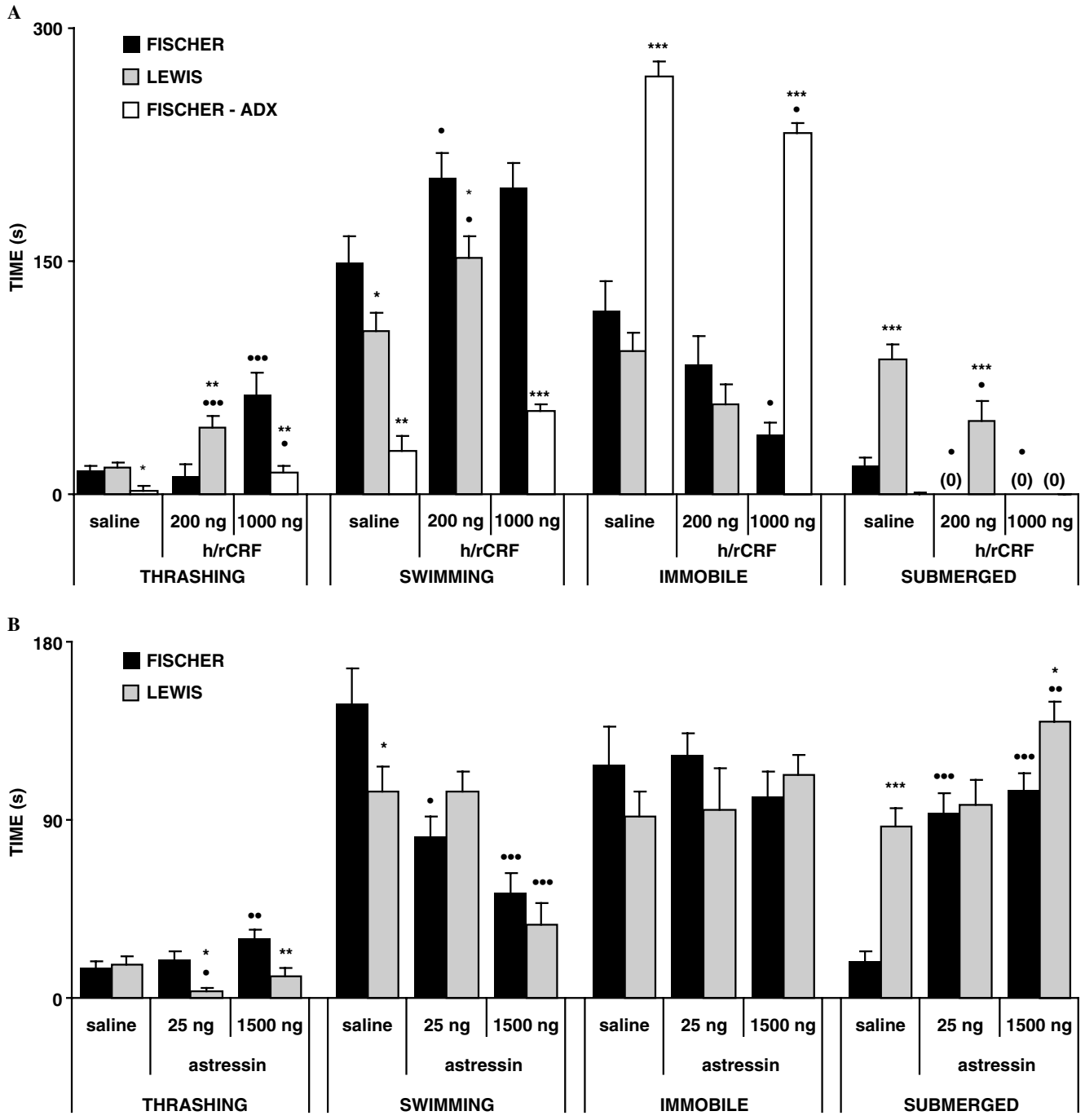


Fig. 10. Differences between Fischer (black columns), Lewis rats (gray columns), and adrenalectomized Fischer rats (white columns) and effect of i.c.v. h/rCRF (A) or astressin (B) in the forced swim test. Lewis rats often stopped swimming and spent more time than Fischer rats submerged. In Fischer rats, adrenalectomy increases the time spent immobile and abolishes the time spent thrashing and submerged. Injection of h/rCRF or astressin was carried out 20 min before testing. Asterisks (*) represent the significance between strains. $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$. Dots (•) represent the difference of drugs compared to saline-injected animals. $^{\bullet}P < 0.05$, $^{\bullet\bullet}P < 0.01$, and $^{\bullet\bullet\bullet}P < 0.001$. Results from sham-adrenalectomized Fischer rats were similar to those from intact animals and are not represented in the figure.

ina, 2003; Vissers et al., 2004). This is unlikely since many of the behavioral effects of CRF are maintained after hypophysectomy (Morley and Levine, 1982; Veldhuis and De Wied, 1984; Eaves et al., 1985; Fekete et al., 1985; Berridge and Dunn, 1989) and the circulating levels of corticosterone did not correlate with the pain behavior in the present experiments. It should be noted that the increase in corticosterone levels in Lewis rats following either CRF or astressin injection probably results from the mixed excitatory (Herman and Cullinan, 1997; Cook,

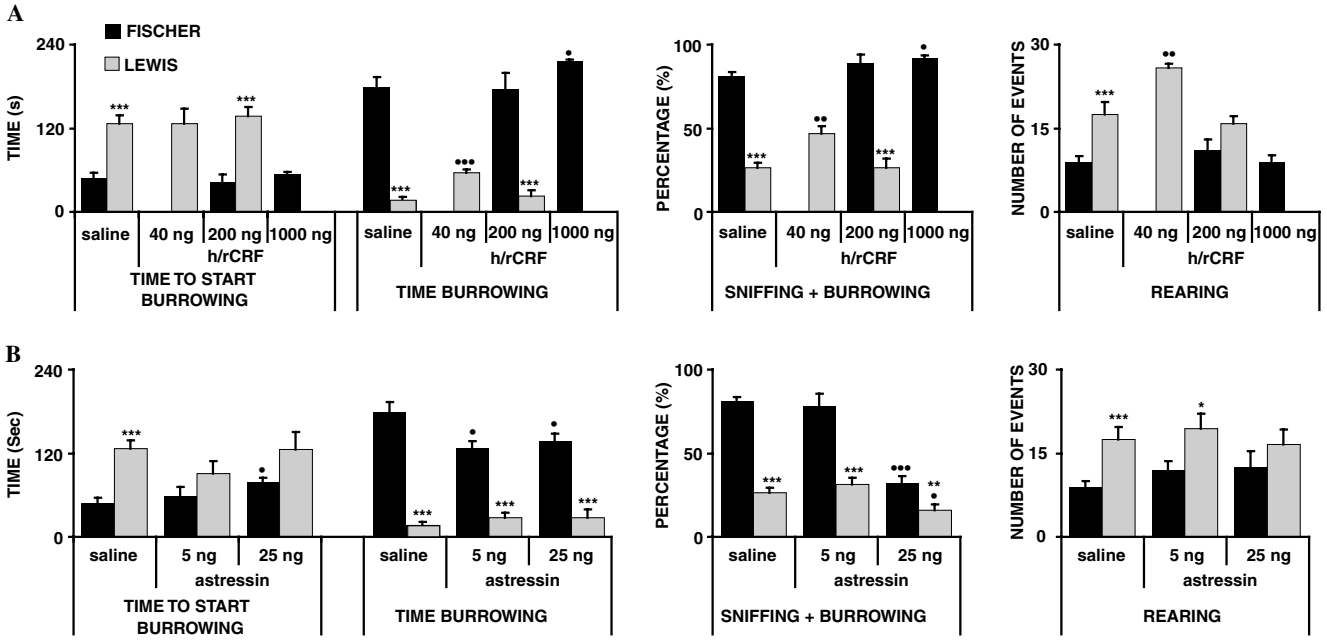


Fig. 11. Differences between strains and effect of h/rCRF (A) or astressin (B) in the predator odor test. Fischer rats start burrowing sooner and for longer than Lewis rats. i.c.v. injections of h/rCRF or astressin were carried out 20 min before testing. CRF increases and astressin decreases stress behavior in both Fischer and Lewis rats but Lewis rats require a lower dose of h/rCRF and higher dose of astressin to elicit an effect. Asterisks (*) represent the significance between strains. $^{**}P < 0.01$, $^{***}P < 0.001$. Dots (•) represent the difference of h/rCRF or astressin compared to saline-injected animals. $^{\bullet}P < 0.05$, $^{\bullet\bullet}P < 0.01$ and $^{\bullet\bullet\bullet}P < 0.001$.

2004) and inhibitory (Herman and Cullinan, 1997; Cole and Sawchenko, 2002; Bartanusz et al., 2004) effects that forebrain CRF has on GABAergic interneurons projecting to the CRF containing neurons in the hypothalamic paraventricular nucleus.

4.2. Other substrates for the antinociceptive effect of CRF

Evidence that CRF is antinociceptive by activating descending pain inhibitory circuits to the spinal cord comes from our finding that the interphase of the formalin test was accentuated by CRF and blocked by astressin. The interphase is thought to result from the activation of the endogenous pain inhibitory system (Henry et al., 1999). However, descending inhibition is usually associated with a decrease in evoked *c-fos* expression in nociceptive areas of the spinal cord (Gogas et al., 1996; Ohashi et al., 2003). In contrast, in our study, i.c.v. CRF did not change the number of activated spinal neurons (Fos positive) in Lewis rats and increased the number in Fischer rats despite an antinociceptive effect. This finding does not entirely rule out the possibility of descending inhibition because there could be a discrepancy between *c-fos* expression and pain behavior (Harris, 1998) due to Fos expression in neurons such as GABAergic inhibitory interneurons not involved in nociceptive activation (Puskar et al., 2001).

CRF receptors occur throughout the brain (Potter et al., 1994; Van Pett et al., 2000) and offer many targets where CRF might act to change pain behavior. Following i.c.v. administration, CRF reaches high concentrations in pain relevant regions such as the hypothalamus, amygdala, septum, periaqueductal gray matter (PAG), and locus coeruleus (Bittencourt and Sawchenko, 2000). In the amygdala, CRF tonically inhibits pain behavior (Cui et al., 2004), while in the locus coeruleus, CRF1 receptors activate noradrenergic neurons (Emoto et al., 1993; Curtis et al., 1997; Lejeune and Millan, 2003) that mediate stress analgesia (Jasmin et al., 2003; Tsuruoka et al., 2004). CRF might act via the hypothalamus (Imaki et al., 2001) to stimulate oxytocin neurons that have antinociceptive effects (Robinson et al., 2002) or activate neurons projecting to the PAG influencing responses to escapable and inescapable nociceptive stimuli (Lumb, 2001).

While our study shows an analgesic effect of central CRF on somatic pain, it should be noted that CRF can trigger visceral pain and inflammation (Bunnett, 2005; la Fleur et al., 2005). This hyperalgesic effect appears to involve the cholinergic parasympathetic system (Tache et al., 2004).

4.3. Strain differences in the pain modulating effects of CRF

The similar nociceptive thresholds between Fischer and Lewis on the first day of testing agree with published results (Lovell et al., 2000) but differences in

nociceptive thresholds between strains became apparent with repeated nociceptive testing as has been reported for other stressors (Dhabhar et al., 1997). The decrease in mechanical paw withdrawal values in Lewis rats is probably due to the loss of endogenous non-opioid analgesia (Ren and Dubner, 1996; MacArthur et al., 1999) since naltrexone-induced hyperalgesia was still present after repeated testing.

If the decreased threshold of Lewis rats reflects sensitization of nociceptive pathways after repeated testing, we would have expected CFA to have different effects in both strains. However, when CFA was injected after five testing sessions, a similar decrease of thresholds in both Fischer and Lewis rats was recorded and this occurred when paw withdrawal latencies were lower in Lewis rats.

Strain differences were also observed in the pain modulating effects of CRF and astressin. Lewis rats responded to lower doses of CRF while Fischer rats responded to a lower dose of astressin. Because Lewis rats have lower levels of stress-induced CRF synthesis (Calogero et al., 1992; Sternberg et al., 1992; Grota et al., 1997), the occupancy of CRF receptors is lower, we hypothesize that less exogenous CRF is needed to produce an effect. In Fischer rats, astressin has a greater effect, because the CRF receptor occupancy is higher.

Some strain differences might reflect variations in distribution and density of CRF and corticosteroid receptors in the forebrain (Lahmame et al., 1997; Jongen-Relo et al., 2002). In addition to CRF, Lewis rats present altered hypothalamic responses to acetylcholine, noradrenaline, and serotonin (Calogero et al., 1992; Lahmame et al., 1997; Paulus et al., 1998).

4.4. Responses to stressful stimulus do not reflect affective susceptibility to pain

Because they had a lower score on the anxiety/fear tests, we expected that Lewis rats would habituate to the novelty of the testing environment and stimulus (Brudzynski and Ociepa, 1992) and display less affective-like behaviors, yet the opposite occurred. Lewis rats began vocalizing, which is considered to be an affective response to noxious stimulation (Levine et al., 1984; Jourdan et al., 1998; Onen et al., 2000; Pelissier et al., 2003), at a time when much of their non-opioid-dependent stress analgesia was gone. Therefore, these rats with low scores on anxiety/fear testing can still have increased affective/emotional-like responses towards the nociceptive stimulus and/or the conditions in which it is delivered.

Lewis rats vocalized when there was a decrease in the nociceptive threshold, which suggests a form of anxiety-like behavior conditioned specifically by the nociceptive stimulus (Vidal and Jacob, 1986; Borszcz, 1993). Continual handling did not produce any vocalization, except during nociceptive testing sessions and sometimes preceding the stimulus. Furthermore, the anxiolytic drug diazepam had an antinociceptive effect and CRF increased the number of vocalizations despite also increasing the nociceptive threshold. CRF, however, does not appear directly involved in the genesis of the stimulus-induced vocalization since Fischer rats never vocalized, whether treated with CRF or astressin.

There is disagreement over whether the pain reported by FMS patients results from increased response to stress or other psychological issues (Van Houdenhove and Egle, 2004). Interestingly, Lewis rats and rats treated with astressin show an impaired stress response per se but nonetheless have increased pain susceptibility. This models the self-description of many FMS patients and some of their biological anomalies (Mease, 2005).

5. Conclusion

Our finding supports the growing consensus (Lariviere and Melzack, 2000) that central CRF is analgesic and, by extension, might have a direct role in pathogenesis of certain pain disorders. The mechanisms by which central CRF modulates pain might be neural and hormonal and influenced by phylogeny and individual experience. The antinociceptive effects of CRF raise the possibility that CRF1 antagonists for treating depression (Nemeroff, 2002; Zorrilla and Koob, 2004) might increase pain in some patients.

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ABSTRACTS 2005

Abstracts #1-2

American Pain Society (APS)
Boston, MA, March 30 – April 2, 2005

Abstracts #3-4

International Association for the Study of Pain (IASP)
11th World Congress on Pain
Sydney, Australia, November 12-17, 2005

Abstracts #11-12

American College of Rheumatology (ACR)
San Diego, CA, November 12-17, 2005

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Site Guide

Annual Meeting

Perform a new search

Year: 2005

Poster #: 672

Title: Association between experimental and clinical pain measures in persons with fibromyalgia and chronic fatigue syndrome

Authors: M. Geisser, D. Clauw, D. Williams, R. Patel, R. Gracely; University of Michigan, Ann Arbor, MI

Classification: Disease Entities (Human)

Themes: C07 - Myofascial Pain & Fibromyalgia

Description:

Evoked pain is often used as a model for the study of clinical pain, yet there is little data regarding the relationship between the two. In addition, there is little data regarding the types of stimuli and stimulus intensities that are most closely related to clinical pain. In this study, 38 subjects who fulfilled the criteria for a diagnosis of fibromyalgia (FM), chronic fatigue syndrome (CFS), or both syndromes were administered measures of clinical pain. In addition, subjects underwent experimental testing utilizing heat and pressure stimulation. Stimulation levels evoking low, moderate and high intensity and comparable levels of unpleasantness were determined for both types of stimuli using random staircase methods. Clinical pain was assessed using visual analogue ratings of “pain during the past month” and “pain today”, in addition to the present pain intensity and total pain rating index from the short form of the McGill Pain Questionnaire (MPQ). Heat was not significantly associated with clinical pain ratings, with the exception of unpleasantness ratings at high stimulus intensities. Both intensity and unpleasantness ratings of pressure were significantly associated with clinical pain at low, moderate and high levels, and the strength of the association increased at higher stimulus intensities. For example, the association between MPQ scores and pressure stimulation was -.44 ($p < .01$) at ratings of low intensity, -.49 ($p < .01$) at ratings of moderate intensity, and -.52 ($p < .01$) at high intensities. These findings suggest that pressure stimulation as an experimental pain model in these

populations more closely reflect the clinical pain for these conditions. This likely reflects the fact that FM as a clinical syndrome is characterized primarily by tenderness. These findings merit consideration when designing experimental studies of FM and CFS.

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Annual Meeting

Perform a new search

Year: 2005

Poster #: 673

Title: fMRI analysis of innocuous pressure in patients with fibromyalgia

Authors: R. Patel, D. Clauw, R. Gracely; Department of Medicine, Division of Rheumatology, Department of Neurology, University of Michigan, Ann Arbor, MI

Classification: Disease Entities (Human)

Themes: C07 - Myofascial Pain & Fibromyalgia

Description:

Painful pressure applied to the thumb for 25s by a 1 cm diameter probe results in a painful sensation related to the magnitude of pressure. This function in 13 healthy control subjects was used to divide 22 patients with fibromyalgia (FM) into sensitive (n=10) and insensitive (n=12) FM patients. The present study evaluated whether differences in sensitivity extended also to non-painful, innocuous stimulus pressures. Intermingling innocuous pressures with painful pressures in a random order also assessed the influence of pain expectation and anticipation, which has been shown to independently evoke brain activity. The 22 patients participated in a 10-min fMRI session in which innocuous pressures (typically 0.5 kg) and pressures sufficient to evoke painful sensations rated as mild, moderate or intense were applied to the thumb during alternating 25s blocks of painful pressure and pressure release. Scans were performed at 5s intervals and the scans for each pressure were compared to the off scans. In both groups, innocuous pressure was associated with cerebral activation in contralateral secondary somatosensory cortex and inferior parietal lobule. In addition, sensitive patients showed unique activations in primary somatosensory cortex, insula and middle frontal gyrus that were not observed in insensitive patients, and insensitive patients showed unique activations in bilateral temporal lobes and in ipsilateral middle frontal gyrus. However, statistical comparison of both groups showed only significantly greater activation in ipsilateral middle

frontal gyrus in the sensitive patient group. The observation of possibly enhanced cerebral response to innocuous stimulation in the sensitive group suggests that the previously observed augmentation of painful pressure may extend to pressures described as non-painful. Further studies are needed to evaluate whether the common activation in association areas represents an effect of physical stimulation or expectations/anticipation of painful stimulation during the random stimulus series.

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Program Number: 1254-P124 **Day / Time:** Thursday, Aug. 25, 8:30 AM - 5:30 PM

Pain processing differences in women with fibromyalgia with and without a self - reported history of physical or sexual abuse

S.A.McLean [1]; R.Patel [2]; D.A.Williams [2]; D.J.Clauw [2]; R.H.Gracely [2]

1. Emergency Medicine, University of Michigan Medical Center, Ann Arbor, MI, USA; 2. Internal Medicine, University of Michigan Medical Center, Ann Arbor, MI, USA

Aim of Investigation: We have previously identified neurobiological differences in women with fibromyalgia (FM) with and without a self-reported history of childhood physical or sexual abuse. The objective of this study was to compare pain processing in these two groups using functional Magnetic Resonance Imaging (fMRI).
Methods: Pressure sufficient to cause self-reported slightly intense pain (13.5/20) was applied to the left thumbnail of FM patients with (n = 8) and without (n = 9) a history of abuse. Echo-planar images with TR = 5s, TE 40 ms, 90 degree flip angle, 64x64 matrix, and 192 FOV over 50 horizontal 3mm slices were obtained with a Siemens 1.5 Tesla scanner. Images were corrected for head motion, realigned to a standard template, spatially smoothed with a Gaussian filter and intensity normalized. Analyses compared scans acquired during the 25 s pain stimulus to those acquired during a subsequent 25 s resting period.
Results: In comparison to FM patients who did not report a history of childhood physical or sexual abuse, FM patients reporting a history of abuse had significantly increased activations in contralateral insula, putamen, and superior and medial frontal gyrus, and ipsilateral S2, medial frontal gyrus, middle temporal gyrus, and cerebellum. Significant differences were also found in bilateral periaqueductal gray. (PAG).
Conclusions: A self-reported history of physical or sexual abuse is associated with variations in pain processing in FM.
Acknowledgements: Supported by NIH K12 RR017607-01 and DAMD-17002-0018

Citation: S.A.McLean, R.Patel, D.A.Williams, D.J.Clauw, R.H.Gracely. Pain processing differences in women with fibromyalgia with and without a self - reported history of physical or sexual abuse. Program No. 1254-P124. *2005 Abstract Viewer.* Sydney, Australia: International Association for the Study of Pain

Program Number: 1259-P129 **Day / Time:** Thursday, Aug. 25, 8:30 AM - 5:30 PM

Mechanisms of Task Induced Deactivation in Fibromyalgia

R.Patel ; J.Glass; D.J.Clauw; R.H.Gracely SPON: Richard H. Gracely

Internal Medicine - Rheumatology, University of Michigan, Ann Arbor, MI, USA

Aim of Investigation: Neuroimaging studies of pain focus on stimulus-evoked increases in activity and infrequently address 'task induced deactivation' (TID). This study compared TIDs in 25 fibromylagia patients (FM) and 15 healthy controls (HC) and evaluated if TIDs represent the effects of attention during painful stimulation, or the effects of spontaneous thought or 'relief' after stimulation, by assessing the influence of the magnitude of evoked pain on subsequent off (OFF) activity during the absence of stimulation.

Methods: Subjects received fMRI scans every 5 s for 10 min. Pressures calibrated to evoke innocuous touch, or mild, moderate or slightly intense pain, were applied to the left thumb by a 1 cm diameter probe in random sequence during alternating 25 second blocks of painful pressure and pressure release.

Results: BOLD analysis revealed robust TIDS in FM in prefrontal cortex (PREF; Z = 8.32) and in ipsilateral primary somatosensory cortex (SI; Z = 8.03) that were significantly greater than TIDS in HC ($P < 0.001$). Pain magnitude in FM and HC was non-significantly correlated with OFF activity in PREF, significantly inversely correlated with OFF activity in putative pain regions (contralateral SI, SII , ACC, insula), and uncorrelated with OFF activity in ipsilateral SI.

Conclusions: The ipsilateral SI TID likely represents reduced attention during painful stimulation. The positive but moderate association between PREF 'off' activity and preceding pain magnitude suggests a minor role of pain relief mechanisms in the observed PREF TIDs. The novel inverse relationship with pain magnitude and subsequent activity in pain processing regions is consistent with either a fast acting suppression induced by painful stimulation or a sensory persistence evoked by less painful or innocuous sensations. Future studies of these effects in control subjects and FM patients may provide evidence for the poorly understood mechanisms of pain augmentation in FM.

Acknowledgements: Supported by Cooperative Agreement DAMD 17-002-0018

Citation: R.Patel, J.Glass, D.J.Clauw, R.H.Gracely. Mechanisms of Task Induced Deactivation in Fibromyalgia. Program No. 1259-P129. *2005 Abstract Viewer.* Sydney, Australia: International Association for the Study of Pain

Title: Time Course of Pressure Task-Induced Deactivations in Fibromyalgia and Healthy Controls

Category: 9. Fibromyalgia and soft tissue disorders

Author(s): Rupal Patel, Jennifer Glass, Daniel J. Clauw, Richard H. Gracely. University of Michigan, Ann Arbor, MI

Presentation Number: 118

Poster Board Number: 118

Introduction: We have demonstrated decreased brain activity evoked by painful pressure in the Medial Frontal Gyrus (MFG) in patients with fibromyalgia (FM). This task-induced deactivation (TID) was hypothesized to represent interruption of spontaneous thought and relief from the evoked painful pressure. The current study evaluated and compared the time course of TID in the MFG in FM patients and in healthy control (HC) subjects

Methods: During 10 min fMRI sessions, pressures calibrated to evoke mild, moderate and slightly intense pain were applied to the thumb by a 1 cm diameter probe in random sequence during alternating 25s blocks of painful pressure and pressure release. Twenty-two FM and 13 HC received fMRI scans performed at 5s intervals. Analysis of the BOLD signal (head motion correction, spatial smoothed 6mm FWHM, intensity normalization, conversion to standard coordinate system, statistical comparison of pressure and pressure release conditions) was performed using Medx.

Results: In FM, the fMRI signal in MFG during application of the High and Medium stimulus was significantly less than in the subsequent stimulus off conditions ($p<0.05$), while there was no significant difference between these conditions in HC. The decrease in the on condition was greater for FM than HC, and the increase in the off conditions was also greater for FM than HC (all $p <0.05$). In FM within a condition, the fMRI signal decreased during stimulation and increased after stimulation with rates associated with stimulus pressure. Slopes of linear regressions for innocuous, mild, moderate and intensely painful pressure were 0.007, 0.026, -0.065, -0.366 during stimulation, and -0.060,0.033,0.326,0.327 following stimulation. In HC, there was little variation in fMRI signal during either stimulus on or off conditions, with slopes of 0.051, 0.036, -0.017, -0.106 during stimulation, and -0.046, -0.145, 0.076, 0.041 following stimulation.

Conclusion: In FM, TIDs to painful pressure may represent a behavioral measure of pain magnitude corresponding to sensitive animal models of response suppression. The present results in the MFG suggest that this method grades stimulus pressure and/or subjective pain in FM. This result is consistent with a disruption of spontaneous thought but the time course of activity during the off period does not support an effect of a positive “relief” mechanism. These TID effects were robust in FM but not in HC, suggesting that fMRI measures of disruption of ongoing thought may provide a novel sign of FM and related disorders.

Title: **Auditory perceptions in patients with fibromyalgia : Is fibromyalgia due to a more global problem with sensory processing?**

Category: 9. Fibromyalgia and soft tissue disorders

Author(s): Ljubinka D. Rajcevska[1], Barbara Patrick[2], Samantha Chriscinske[2], Ananda Sen[3], Richard Gracely[2], Daniel Clauw[4]. [1]University Sts Cyril and Methodius ,FYR Macedonia, Skopje, The former Yugoslav Republic of Macedonia; [2]Chronic Pain and Fatigue Research Center, Ann Arbor, MI; [3]Rackham School, Department of Statistics, Ann Arbor, MI; [4]University of Michigan, Chronic Pain and Fatigue Research Center, Ann Arbor, MI

Presentation Number: F74

Poster Board Number: 568

Purpose: Previous studies have suggested that fibromyalgia (FM) patients report a heightened level of sensitivity to many sensory stimuli (SS), and display a decreased noxious threshold for not just pressure, but also heat, cold and electrical stimuli. However, these studies of sensory threshold have used "ascending" paradigms, influenced by psychological factors, such as expectancy or hypervigilance, which are differentially present in FM patients. Paradigms which present stimuli in a random fashion can reduce or eliminate the influence of these factors. The purpose of this study is to compare the level at which acoustic stimuli presented in random fashion provoke unpleasentness in patients with FM vs. healthy controls (HC). Our hypothesis was that individuals with FM suffer from an overall heightened level of sensitivity to SS vs. HC, and thus will demonstrate increased sensitivity to sound and a lower level of acoustic tolerance. Also, the auditory thresholds will be significantly associated with pressure thresholds collected in the same manner, suggesting a more global problem with sensory processing in individuals with FM.

Methods: The sample consisted of 35 patients, 17 of whom fulfilled the ACR criteria for FM and 18 HC matched for age and gender. A hearing screening test (HST) was performed on both ears according to ASHA guidelines. Loudness Discomfort Levels (LDL) were obtained from all participants, who also completed Pressure and Pain Testing (PPT) performed on one thumb. All participants also completed a Hyperacusis Questionnaire (HQ), indicating their subjective sensitivity to environmental sounds.

Results: The data from the HQ confirm that FM patients report increased sensitivity to sound: 70.6% of FM patients feel that they are sensitive to everyday sound ($p = 0.018$), and 76.5% of patients with FM vs.11.1% of HC wish that they were less sensitive to sound ($p = 0.001$). A regression analysis adjusting for each ear and sensitivity level showed borderline statistical difference in LDL between the two groups ($p = 0.0716$). In the FM group, there were significant correlations between the pressure and auditory thresholds at both levels of sensitivity ($r = 0.57$, $p = 0.027$ for medium and $r = 0.585$, $p = 0.022$ for high). There is not a corresponding significance in the correlations obtained for the HC group.

Conclusion: These data suggest that noxious thresholds to both mechanical and auditory stimuli simmilarly display a "left-shift" in stimulus response function in FM patients vs. controls. These and other data suggest that FM may be due to a more global problem with sensory processing , rather than a more specific problem with pain processing.

ABSTRACTS 2006

Abstract #13

American Pain Society (APS)
San Antonio, TX, May 2 - 6, 2006

Abstract #14-15

European League Against Rheumatism (EULAR)
Amsterdam, Netherlands, June 21-24, 2006

Abstract #17

Society for Neuroscience
Atlanta, GA, October 14-18, 2006

Abstracts #19-31

American College of Rheumatology (ACR)
Washington, DC, November 10-15, 2005

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Annual Meeting

Perform a new search

Year: 2006

Poster #: 698

Title: Impact of co-morbid somatic symptoms above and beyond that of pain in patients with fibromyalgia and gulf war illnesses

Authors: M Geisser, D Williams, D Clauw; University of Michigan, Ann Arbor, MI

Classification: Disease Entities (Human)

Themes: Myofascial Pain & Fibromyalgia

Description:

For disorders such as Fibromyalgia (FM), and to a lesser extent Gulf War Illnesses (GWI), pain is believed to be a defining symptom of the illness. However, a number of co-morbid problems are often present in these illnesses with understudied contributions to the illnesses' impact. In the present study, 49 patients with FM or GWI were asked to indicate all symptoms experienced for a period of 3 months within the past year using a symptom checklist containing 51 symptoms. The sum of all symptoms was then correlated with measures of pain (MPQ), fatigue (MFI), perceived function (SF-36), and memory complaints (MASQ). The mean number of physical complaints was 19.5 (SD = 10.6). Zero-order correlations indicated that greater numbers of physical complaints was significantly associated with higher clinical pain ($r = .38$, $p < .01$), poorer physical functioning ($r = -.45$, $p < .01$), and greater perceived deficits in verbal and visual-spatial memory ($r = .41$, $p < .01$ and $r = .36$, $p < .01$, respectively). Physical complaints were not significantly associated with fatigue. To examine the unique ability of somatic complaints to predict function and perceived memory deficits above and beyond pain, regression analyses were performed. Pain intensity was entered into the regression model first, followed by the sum of physical complaints. These analyses indicated that physical complaints significantly predicted additional variance in perceived function, verbal memory, and visual-spatial memory. These findings suggest that the number of physical complaints observed in these disorders are significantly associated with pain, and are uniquely related to physical function and memory complaints independent

of pain intensity. Additional study of the co-morbid complaints accompanying pain conditions like FM is warranted as they appear to independently contribute to declines in function that are often attributed only to pain.

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[2006] [SAT0340] INCREASED SENSITIVITY TO SOUND AS A FEATURE OF DISTURBED GLOBAL SENSORY PROCESSING IN PATIENTS WITH FIBROMYALGIA

L. Damjanovska Rajcevska[1], A. Sen [2] , P. Kileny [3] , R. Gracely [2] , D.J. Clauw [2] [1]Rheumatology, Clinical Center Skopje, Skopje, The former Yugoslav Republic of Macedonia, [2]Chronic Pain and Fatigue Research Center, [3]Audiology Department, University of Michigan Medical School, Ann Arbor, United States

Background: In recent years studies have shown that fibromyalgia (FM) patients report increased sensitivity to many different sensory stimuli, including somatic and visceral pain, bright lights, odors and loud sounds. Previous experimental studies in FM have primarily focused on testing sensitivity to somatic stimuli and have documented that FM patients exhibit a "left shift" in responsiveness to numerous stimuli, including pressure, heat, cold and electricity.
More advanced experimental pain paradigms performed with pressure and heat pain testing suggest that this left-shift is not simply due to expectancy or hypervigilance, because the hyper-responsiveness is seen even when stimuli are presented in a random paradigm that minimize the influence of psychological state on the test results.
Objectives: The purpose of this study was to concurrently test pressure and sound sensitivity in FM patients and healthy controls (HC)using random testing paradigm and to determine whether there are parallel increases in sensitivity to these two disparate sensory modalities which would suggest a more global problem with sensory processing in individuals with FM.
Methods: Sixty (60) participants,in which sensorineureal hearing loss was excluded by a standardized hearing screening test (HST)were recruited for the study,29 of whom fulfilled the ACR criteria for FM. Thirty one (31)HC were matched for age and gender. Acoustic stimuli (a pure tone of 2000 Hz ranging in intensity from 40-100 dB) were presented to the participants in random order fashion and the participants were asked to rate the loudness for each ear. Pressure pain testing (PPT) was performed using parallel paradigms, on one thumb. Participants rated the loudness and pressure intensity and unpleasantness they felt on a Gracely box scale (0-20).All participants also completed a Hyperacusis Questionnaire (HQ) indicating their subjective sensitivity to environmental sounds as well as SF-36 and Mc Gill Pain Questionnaire-Short Form (MGPQ-SF).
Results: The data from the HQ showed that 26(89.6%) of the FM patients reported increased sensitivity to sound vs. 5 (19.3%)HC.Sixteen(55.1%)patients with FM reported ringing in the ears(tinnitus).The auditory tresholds for low, medium and high sensitivity were 5-13 dBs lower in patients with FM then in HC, which was significantly different at medium and high sensitivity, for both ears, between the two groups. (p=0.011 and p=0.001 for the first ear and p=0.019,p=0.014 for the second ear tested).As expected, there was also a significant difference in PPT between the two groups(p=0.001 for low and medium sensitivity and p=0.049 for high sensitivity).
Conclusion: Increased sensitivity to sound,unusual intolerance to ordinary environmetal sounds and ringing in the ears are common complaints in FM patients, even though they usually do not have any clinically and audiologically detectable ear disease. These data suggest that at least some FM patients have a generalized sensitivity to different sensory stimuli as a feature of disturbed global sensory processing,i.e.interoception.
References: 1. Yilmas M,Baysal E et al.Assessment of the ear and otoacoustic emission findings in FM syndrome.Clin Exp Rheumatol.2005 Sep-Oct;23(5):701-703
2. Petzke F,Clauw DJ,Gracely RH.Increased pain sensitivity in FM:effects of stimulus type and mode of presentation.Pain 2003;105(3):403-413

Fibromyalgia

[2006] [SAT0341] IS FIBROMYALGIA DUE TO A DISTURBANCE IN PAIN PROCESSING, OR A MORE GLOBAL PROBLEM WITH SENSORY PROCESSING?

L. Damjanovska Rajcevska[1], A. Sen [2] , P. Kileny [3] , R.H. Gracely [2] , D.J. Clauw [2] [1]Rheumatology Department, Clinical Center Skopje, Skopje, The former Yugoslav Republic of Macedonia, [2]Chronic Pain and Fatigue Research Center, [3]Audiology Department, University of Michigan Medical School, Ann Arbor, United States

Background: In recent years studies have shown that fibromyalgia (FM)patients report increased sensitivity to many different sensory stimuli, including somatic and visceral pain, bright lights,odors and loud sounds. Previous experimental studies in FM have primarily focused on testing sensitivity to somatic stimuli and have documented that FM patients exhibit a "left shift" in responsiveness to numerous stimuli, including pressure,heat,cold and electricity.
More advanced experimental pain paradigms performed with pressure and heat pain testing suggest that this left-shift is not simply due to "expectancy" or "hypervigilance", because the hyper-responsiveness is seen even when stimuli are presented in a random paradigm that minimize the influence of psychological state on the test results.
Objectives: The purpose of this study was to concurrently test pressure and noise sensitivity in FM patients and healthy controls (HC)using random testing paradigm and to determine whether there are paralel increases in sensitivity to these two disparate sensory modalities which would suggest a more global problem with sensory processing in some individuals with FM.
Methods: Sixty (60) participants in which sensorineureal hearing loss was excluded by a standardized hearing screening test (HST)were recruited for the study,29 of whom fulfilled the ACR criteria for FM.Thirty one (31)HC were matched for age and gender. Acoustic stimuli (a pure tone of 2000 Hz ranging in intensity from 40-100 dB) were presented to the participants in random order fashion and the participants were asked to rate the loudness for each ear. Pressure pain testing (PPT) was performed using parallel paradigms,on one thumb. Participants rated the loudness and pressure intensity and unpleasantness they felt on a Gracely box scale (0-20).All participants also completed a Hyperacusis Questionnaire (HQ) indicating their subjective sensitivity to environmental sounds as well as SF-36 and Mc Gill pain Questionnaire Short Form (MGPQ-SF).
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Conclusion: Increased sensitivity to sound,unusual intolerance to ordinary environmetal sounds and ringing in the ears are common complaints of FM patients, even though they usually do not have any clinically and audiologically detectable ear disease. These data suggest that at least some FM patients have a generalized sensitivity to different sensory stimuli as a feature of disturbed global sensory processing,i.e.interoception.
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2. Petzke F,Clauw DJ,Gracely RH et al.Increased pain sensitivity in FM:effects of stimulus type and mode of presentation.Pain 2003;105(3):403-413

Fibromyalgia

Program#/Poster#:	247.17/Q14
Title:	Dynamic DNIC activation of vPAG in human subjects
Location:	Georgia World Congress Center: Halls B3-B5
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Painful stimulation applied to animals or humans produces a widespread analgesia termed “diffuse noxious inhibitory controls” (DNIC), that may act via a spinal-brainstem loop. This study used fMRI to assess the effects of DNIC on brainstem activity. Ten subjects (mean age 45) received two pairs of 6-min fMRI scans. In all four 6-min scans, 3 levels of painful (faint, moderate, slightly intense) test pressures were applied to the left thumb in random sequence during alternating 25s blocks of painful pressure and pressure release. In the second 6-min scans of the two pairs, a DNIC stimulus was delivered to the right thumbnail at either a level sufficient to evoke moderately intense pain, or a level evoking only an innocuous pressure sensation. Order of DNIC pairs (painful, innocuous) was randomized across subjects. fMRI data were acquired by a 3.0 Tesla GE Signa scanner (LX [VH3] release, Neuro-optimized gradients (FOV = 22, slice thk/sp = 3/0, T2*-weighted, single-shot, reverse spiral acquisition, GRE, TR = 2500, TE = 30, FA = 90, 64 x 64). Analysis of the BOLD signal (head motion correction, slice timing corrections, spatial smoothed 6mm FWHM, intensity normalization, conversion to standard coordinate system, statistical comparison of pressure and pressure release conditions) was performed using Medx. In comparison to the pre DNIC baseline, the DNIC manipulation resulted in an increase in left-thumb pain-evoked activity in ventral periaqueductal gray (vPAG, Taliarach coordinates: -6 -14 -4, Z = 4.27). This effect was not observed during the innocuous DNIC control (Z = 0.749). Painful DNIC manipulation resulted in significant activation in vPAG to a periodic 25s on/25s off pressure stimulus in comparison to either no DNIC stimulation or to an innocuous DNIC control stimulation. This fast enhancement of pressure pain-induced activity suggests synchronous, dynamic activation of pain modulatory systems.

Disclosures: **R.H. Gracely**, None; **R. Patel**, None; **S.E. Harte**, None; **D.J. Clauw**, None.

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Increased Symptoms of Pain, Fatigue, Cognitive Problems and Negative Mood after Exercise Deprivation and Sleep Restriction are Predicted By Baseline Autonomic and HPA Function

Author Block: Jennifer M. Glass[1], Angela K. Lyden[1], Cathryn J. Byrne-Dugan[1], Angela K. Gupta[1], Brian M. Renard[1], Kirsten R. Ambrose[1], Kimberly H. Groner[1], Suzie As-Sanie[2], Dina Dadabhoy[1], David A. Williams[1], Daniel J. Clauw[1]. [1]Departments of Internal Medicine/Rheumatology, University of Michigan, Ann Arbor, MI; [2]Department of Obstetrics/Gynecology, University of Michigan, Ann Arbor, MI

Introduction. Chronic pain disorders such as fibromyalgia are often precipitated by an event that prevents normal sleep and exercise. We hypothesize that sleep restriction and exercise deprivation can act as stressors, and that neurobiological factors can predict if an otherwise healthy individuals will respond to such stress with an acute increase in symptoms of pain, fatigue, cognitive problems and negative mood.
Method. In an ongoing study, the initial 36 participants are the subject of this report. These healthy adults (ages 18-41 years) ran at least five times per week and slept 7-9 hours per night. Subjects were randomly assigned to one of four groups: control (normal activity and sleep), exercise deprivation, sleep restriction (6 contiguous hours in bed per night), or both exercise and sleep restriction. The deprivation period lasted 10 days. At baseline and near the end of the deprivation period somatic symptoms, heart rate variability (HRV; ultra-low frequency, very-low frequency, and total power) and salivary cortisol (taken in the morning after awakening) were obtained. Pearson product moment correlations were calculated to assess the association between baseline HRV and am cortisol measures and changes in symptoms (deprivation minus baseline).
Results. Strong negative correlations were observed between the HRV measures and changes in self-reported pain (McGill sensory, present pain index and VAS; r values between -.260 and -.706); between HRV measures and changes in cognitive performance (PVT and word-list recall; r values between -.270 and -.534). Strong negative correlations were observed between am cortisol and changes in mood (CESD, anxiety, Profile of Mood States; r values between -.306 and -.599); between am cortisol and change in fatigue (Multidimensional Fatigue Index-general, r = -.457); and between am cortisol and changes in cognitive performance (PVT, r = -.466 and word-list recall, r = -.542).
Conclusions. These results confirm that baseline physiological measures can predict subsequent increases in symptoms after sleep and exercise restriction, and are consistent with the hypothesis that low HPA and ANS function represent a diathesis that predisposes individuals to development of somatic and cognitive symptoms after exposure to a stressor.
Author Disclosure Block: **J.M. Glass**, None; **A.K. Lyden**, None; **C.J. Byrne-Dugan**, None; **A.K. Gupta**, None; **B.M. Renard**, None; **K.R. Ambrose**, None; **K.H. Groner**, None; **S. As-Sanie**, None; **D. Dadabhoy**, None; **D.A. Williams**, None; **D.J. Clauw**, DAMD 17 00 2 0018, 2; Cypress Biosciences, 5.

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DNIC Activation of vPAG is Absent in Fibromyalgia

Author Block: Richard H. Gracely[1], Rupal Patel[1], Greta A. Naylor[1], Brian K. Michalik[1], Matthew Gonzalez[2], Daniel J. Clauw[1]. [1]Departments of Internal Medicine/Rheumatology, University of Michigan, Ann Arbor, MI; [2]University of Michigan, Ann Arbor, MI

Introduction: Application of a pain stimulus in animals and humans produces a widespread analgesia termed "diffuse noxious inhibitory controls" (DNIC). DNIC has been noted to be deficient in several studies of patients of fibromyalgia (FM). This association with a lack of intrinsic analgesia and augmented pain sensitivity suggest that a defect in intrinsic analgesia may mediate the pain and hyperalgesia in FM. Intrinsic analgesic systems such as DNIC have been localized in the brainstem. This study used fMRI to assess the effects of DNIC on brainstem activity in FM and healthy controls (HC).
Methods: Eleven female patients (mean age = 45) satisfying ACR criteria for FM and 10 matched HC (mean age = 45) participated in two sessions. Before fMRI scanning, the effects of painful pressure applied to the left thumbnail were assessed using the Multiple Random Staircase method and a verbal-numerical Box pain scale which determined stimulus pressures sufficient to evoke subjective levels of mild, moderate or intense pain sensations. During 6 min fMRI scans, these pressures were applied to the thumbnail in random sequence during alternating 25s blocks of painful pressure and pressure release. In one 6-min scan, a DNIC pressure stimulus was delivered to the right thumbnail at a level sufficient to evoke moderately intense pain. fMRI data were acquired by a 3.0 Tesla GE Sigma scanner (LX [VH3] release), Neuro-optimized gradients (FOV = 22, T2*-weighted, single-shot, reverse spiral acquisition, GRE, TR = 2500, TE = 30, FA = 90, 64 x 64). Analysis of the BOLD signal (head motion correction, slice timing corrections, spatial smoothed 6mm FWHM, intensity normalization, conversion to standard coordinate system, statistical comparison of pressure and pressure release conditions) was performed using Medx.
Results: Comparing DNIC to pre-DNIC baseline in HC, the most significant effect of pain evoked activity was observed in ventral periaqueductal gray (vPAG, Talairach coordinates: 6 14 -4, Z=4.27). Similar brain stem activations (DNIC -pre DNIC baseline) were not observed in FM. A statistical comparison of the DNIC effect between groups using a random effects model showed significantly greater activity in vPAG (4, -16 -6, Z=3.49) in HC, and less activity in regions implicated in pain processing (contralateral primary somatosensory cortex, Z=3.31; cerebellum, Z=3.09; Inferior parietal lobule (BA 40), Z=2.69; Thalamus (Medial Dorsal Nucleus), Z=2.63; secondary somatosensory cortex, Z=2.57).
Conclusion: A large body of evidence indicates that the vPAG is involved in intrinsic descending analgesia. The demonstration of vPAG activation only in HC and decreased activity in pain processing regions in HC is consistent with previous demonstrations of

defective DNIC in FM and suggests that this defect is associated with dysfunction of the intrinsic descending vPAG-mediated system.
Author Disclosure Block: **R.H. Gracely**, Pierre Fabre, 5; **R. Patel**, None; **G.A. Naylor**, None; **B.K. Michalik**, None; **M. Gonzalez**, None; **D.J. Clauw**, DAMD 17 00 2 0018, 2; Cypress Biosciences, 5.

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Accentuated Pain Processing Despite Decreased mu-Opioid Receptor (MOR) Availability in Fibromyalgia

Author Block: Richard E. Harris[1], David J. Scott[2], Greta A. Naylor[1], John B. Romond[1], Adrielle R. Bradford[1], Dina Dadabhoy[1], Richard H. Gracely[1], Jon-Kar Zubieta[3], Daniel J. Clauw[1]. [1]Departments of Internal Medicine/Rheumatology, University of Michigan, Ann Arbor, MI; [2]Molecular and Behavioral Neuroscience Institute, University of Michigan, Ann Arbor, MI; [3]Psychiatry, Radiology, and Mental Health Research Institute, University of Michigan, Ann Arbor, MI

Purpose: Amplification of central neural pain pathways and dysfunction of endogenous antinociceptive mechanisms have both been implicated in fibromyalgia (FM). Here we investigate these two processes using two divergent brain imaging methods within the same participants.
Methods: PET - 11 female FM patients (ages 27-68) and 11 age- and sex-matched pain free controls (ages 21-55) underwent a positron emission tomography scan with [^{11}C]carfentanil, a MOR selective radiotracer. Logan plots were created to obtain maps of whole-brain MOR binding potential (BP) at baseline. [^{11}C]carfentanil binding was assessed using SPM99, and regions showing significant differences in BP between patients and controls were extracted using locally developed software. Correlations between pain report and MOR occupancy were performed in SPSS. fMRI - The same 11 FM patients were age- and sex-matched to a separate group of 19 pain free controls (ages 23-58). Participants underwent a functional magnetic resonance imaging session wherein multiple pressures were applied to the thumbnail bed in pseudo-random order. Pre-processing of images was done with SPM2 and resulting contrast images (2kg/cm^2 pressure vs. no touch) were analyzed at the group level. fMRI activations were correlated with MOR binding using SPSS. Clinical pain intensity and unpleasantness were also assessed.
Results: In the fMRI studies, during pressure pain of equal stimulus intensity, the FM patients exhibited greater neuronal activations in the bilateral insula (right: $p<0.005$; left: $p<0.01$). In the PET studies, FM patients displayed reduced MOR BP in the nucleus accumbens (bilateral: left, $p < 0.0001$; right, $p < .01$) and left amygdala ($p < .02$). Binding within the accumbens was negatively correlated with clinical pain report (GBS: rho=-0.65 to -0.79; all $p<0.05$). Interestingly MOR binding in the left amygdala (rho=-0.68; $p<0.05$), but not the nucleus accumbens ($p>0.5$), was negatively correlated with evoked pain fMRI activations within the insula.
Conclusion: Even though FM patients exhibited augmented central pain processing in the fMRI study, these same patients showed decreased MOR BP in multiple brain regions. This suggests that the augmented pain processing in FM is not due to a attenuated function of the intrinsic opioid system, and also shows the potential value of using multiple functional imaging techniques simultaneously. Furthermore these data

may help explain why FM patients seem to be less responsive to exogenously administered opioids as MOR availability is reduced potentially leading to decreased availability for binding to exogenous ligands.
Author Disclosure Block: **R.E. Harris**, None; **D.J. Scott**, None; **G.A. Naylor**, None; **J.B. Romond**, None; **A.R. Bradford**, None; **D. Dadabhoy**, None; **R.H. Gracely**, Pierre Fabre, 5; **J. Zubieta**, None; **D.J. Clauw**, DAMD 17 00 2 0018, 2; Cypress Biosciences, 5.

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Longitudinal Changes in Pressure Pain Sensitivity Vary with Insular Neuronal Activity in Fibromyalgia Patients

Author Block: Richard E. Harris[1], David J. Scott[2], Greta A. Naylor[1], John B. Romond[1], Adrielle R. Bradford[1], Richard H. Gracely[1], Jon-Kar Zubieta[3], Daniel J. Clauw[1]. [1]Departments of Internal Medicine/Rheumatology, University of Michigan, Ann Arbor, MI; [2]Molecular and Behavioral Neuroscience Institute, University of Michigan, Ann Arbor, MI; [3]Psychiatry, Radiology, and Mental Health Research Institute, University of Michigan, Ann Arbor, MI

Purpose: Previous cross-sectional studies using functional MRI (fMRI) have noted augmented central pain processing in fibromyalgia (FM). However less attention has been paid to fluctuating pain and tenderness levels over time, and how these changes may relate to underlying neural activity. Here we examine longitudinal changes in evoked pressure pain sensitivity in FM, and determined whether changes in this clinical parameter are accompanied by changes in fMRI-measured neural activity.
Methods: 12 female FM patients (ages 27 to 68) were randomized to receive 9 treatments of either acupuncture or sham acupuncture over the course of 4 weeks. For the purpose of this analysis both treatment groups were combined. All participants underwent two fMRI sessions, one before and one after all treatments. During fMRI, multiple pressures were applied to the thumbnail bed in pseudo-random order. Images were pre-processed with SPM2 and resulting contrast images ($2kg/cm^2$ pressure vs. no touch) were analyzed between subjects at both time points. Psychophysical pain testing using pressure stimuli of varying intensities was performed outside of the scanner. fMRI BOLD activations were correlated with psychophysical pressure ratings using SPSS.
Results: Pressure pain sensitivity was significantly reduced following 9 treatments (kg increase mean(sd): 0.30(0.27); $p<0.005$). fMRI BOLD activations in response to pressure pain were reduced after treatment in the contralateral insula ($p<0.005$). Interestingly changes in BOLD activations within both the posterior and anterior insula were negatively correlated with changes in pressure pain sensitivity assessed outside of the scanner (anterior: rho=-0.84; $p<0.005$; posterior: rho=-0.64; $p<0.05$).
Conclusion: These data suggest that long-term changes in evoked pressure pain sensitivity can be achieved in FM. Furthermore, activity within the insula appears to be related to changes in pressure sensitivity. These results have implications for trials in FM, as fMRI activations within the insula could serve as a useful biomarker of pain processing.
Author Disclosure Block: **R.E. Harris**, None; **D.J. Scott**, None; **G.A. Naylor**, None; **J.B. Romond**, None; **A.R. Bradford**, None; **R.H. Gracely**, Pierre Fabre, 5; **J. Zubieta**, None; **D.J. Clauw**, DAMD 17 00 2 0018, 2; Cypress Biosciences, 5.

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Persistent Musculoskeletal Pain and Posttraumatic Stress Disorder Symptoms after Motor Vehicle Collision Share ED Symptom Risk Factors and Outcomes

Author Block: Christoper W. Jones[1], Samuel A. McLean[1], Mark R. Sochor[1], Christopher R. H. Newton[2], Amanda D. Withrow[1], Jennifer Fowler[2], Barbara A. Stanislawski[1], David A. Williams[3], Israel Liberzon[4], Daniel J. Clauw[3]. [1]Emergency Medicine, University of Michigan, Ann Arbor, MI; [2]Emergency Medicine, St. Joseph Mercy Hospital, Ypsilanti, MI; [3]Internal Medicine/Rheumatology, University of Michigan, Ann Arbor, MI; [4]Psychiatry, University of Michigan, Ann Arbor, MI

Purpose: Chronic musculoskeletal pain is common after motor vehicle collision (MVC), but the etiology remains poorly understood. It has been proposed that stress system dysregulation may contribute to the development of both chronic pain and psychological sequelae such as posttraumatic stress disorder (PTSD) after MVC. However, little data is available regarding shared risk factors and outcomes for these disorders.

Material and Methods: Patients being evaluated in the emergency department (ED) after MVC were recruited into an ongoing multicenter study which includes ED baseline assessment and 1-month follow-up evaluation. ED evaluation includes an assessment of post-MVC symptoms such as neck pain, sense of life threat during the collision, and participant completion of the Peritraumatic Distress Scale, a known predictor of PTSD. One month telephone follow-up evaluation assessed the presence of MVC-related neck or back pain symptoms and PTSD symptoms (IES-R). Moderate or severe pain at 1 month was defined by a numeric rating scale score of ≥ 4 on a 0-10 numeric rating scale. Significant PTSD Symptoms were defined by IES-R score ≥ 33. Pain and PTSD outcomes were compared, and correlations between baseline risk factors and 1-month outcomes were calculated.

Results: To date, follow-up data has been obtained in 48 of 49 enrolled patients who have reached the 1-month follow-up time point (98%, 28 female, 20 male, age 18-84, mean 36.4 years). Twelve (21%) reported persistent moderate or severe MVC-related neck pain, 17 (31%) reported moderate or severe MVC-related back pain, 11 (24%) reported significant PTSD symptoms. Persistent MVC-related neck and back pain symptoms were strongly associated with persistent PTSD symptoms ($r = .505$, $p = .000$). Interestingly, ED neck pain score was more strongly associated with 1-month PTSD symptoms ($r = 347$, $p = .016$) than ED Peritraumatic Distress Scale score ($r = .333$, $p = .021$), a known predictor of PTSD.
Conclusion: These pilot data suggest that PTSD and chronic pain symptoms after MVC are frequently co-morbid, and that ED pain symptoms are a strong risk factor for both disorders. Updated information from this ongoing trial will be presented at the meeting.
Author Disclosure Block: C.W. Jones, None; **S.A. McLean**, K12 RR017607-01,

2; **M.R. Sochor**, None; **C.R. Newton**, None; **A.D. Withrow**, None; **J. Fowler**, None; **B.A. Stanislawski**, None; **D.A. Williams**, None; **I. Liberzon**, None; **D.J. Clauw**, DAMD 17 00 2 0018, 2; Cypress Biosciences, 5.

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Additional Keyword (Complete):
: posttraumatic stress disorder (PTSD)

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Pain and Fatigue Symptoms in Healthy Individuals after Sleep and/or Exercise Restriction

Author Block: Angela K. Lyden[1], Jennifer Glass[1], Cathryn J. Byrne-Dugan[1], Brian M. Renard[1], Angela K. Gupta[1], Suzie As-Sanie[2], Dina Dadabhoy[1], David A. Williams[1], Daniel J. Clauw[1]. [1]Departments of Internal Medicine/Rheumatology, University of Michigan, Ann Arbor, MI; [2]Departments of Obstetrics and Gynecology, University of Michigan, Ann Arbor, MI

Introduction. Regular exercise and "good" sleep are salubrious mainstays of overall well-being, regardless of disease state. Despite evidence that sleep hygiene and regular exercise can help manage fibromyalgia symptoms, many find it difficult to incorporate such behaviors into their routine. We speculate that an absence of these behaviors can contribute to exacerbated symptoms, and even acute symptom development among non-patients, and hypothesize that some healthy individuals are prone to fibromyalgia-like symptoms because exposure to a "stressor" (e.g. acute musculoskeletal pain, infection, etc.) causes them to modify their sleep and exercise routines.
Methods. We recruited 36 healthy adults (18-41 yrs) as part of an ongoing exercise and sleep deprivation study. Eligibility required a minimum of 5 days/week and 20 miles (or 4 hr) of running and at least 7-9 hrs sleep/night. Subjects were randomly assigned to one of four groups: control (normal activity and sleep), exercise deprivation, sleep restriction (6 contiguous hours in bed per night), or both exercise and sleep restriction. Each deprivation phase lasted 10 days. We assessed symptom development in 4 domains (pain, mood, fatigue, and cognition) at baseline and between days 7-8 of the deprivation period. Sleep and exercise were entered into a 2-way ANOVA with various symptom outcomes as the dependent variable to evaluate the main effects and interactions of each deprivation category.
Results. There was a significant main effect for sleep on self-report measures across all four symptom domains. Representative measures are reported: Pain (McGill Total Score: $F(1,34)=5.11$, $p<0.05$); Fatigue (POMS Fatigue Scale: $F(1,34)=27.99$, $p<0.0001$); Mood (CES-Depression: $F(1,34)=12.86$, $p<.001$); and Cognition (MASQ- Attention/ Concentration: $F(1,34)=5.59$, $p<.001$). Exercise elicited a non-significant main effect across these same measures ($p>0.05$), and there were no significant interactions ($p>0.05$). Exercise restriction alone had a marginal effect in this sample, though it tended to augment symptom experience with sleep restriction.
Conclusions. Amongst healthy individuals, a subset is prone to acute symptom development following disruption to their normal routine, with the general trend thus far suggesting that a combined sleep/exercise restriction elicits the highest level of symptom increase, followed by sleep restriction alone, and lastly exercise restriction alone.
Author Disclosure Block: **A.K. Lyden**, None; **J. Glass**, None; **C.J. Byrne-Dugan**, None; **B.M. Renard**, None; **A.K. Gupta**, None; **S. As-Sanie**, None; **D. Dadabhoy**,

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Emergency Department Physiologic Predictors of Pain and Psychological Sequelae after Motor Vehicle Collision

Author Block: Samuel A. McLean[1], Michael Switzer[1], Christopher W. Jones[1], Mark R. Sochor[1], Christopher R. H. Newton[2], Amanda D. Withrow[1], Jennifer Fowler[2], David A. Williams[3], Phyllis K. Stein[4], Israel Liberzon[5], Daniel J. Clauw[3]. [1]Emergency Medicine, University of Michigan, Ann Arbor, MI; [2]Emergency Medicine, St. Joseph Mercy Hospital, Ypsilanti, MI; [3]Internal Medicine/Rheumatology, University of Michigan, Ann Arbor, MI; [4]Cardiovascular Division, Washington University, St. Louis, MO; [5]Psychiatry, University of Michigan, Ann Arbor, MI

Purpose: It has been proposed that stress system dysregulation may contribute to the development of both chronic pain and psychological sequelae after motor vehicle collision (MVC). However, the association between emergency department (ED) cortisol levels and high frequency heart rate variability (HF HRV, representing parasympathetic function) and these sequelae has not previously been examined.
Material and Methods: Patients being evaluated in the ED after MVC were recruited into an ongoing multicenter study which includes ED baseline assessment and 1-month outcome evaluation. ED assessment includes salivary cortisol collection and 20 minute Holter monitor recording. Outcome evaluation includes assessment of persistent moderate or severe MVC-related neck or back pain symptoms (numeric rating scale score of ≥ 4 [0-10 scale]), significant PTSD symptoms (IES-R score ≥ 33), and significant depressive symptoms (CES-D ≥ 27). Cortisol samples were assayed using the Diagnostic Products Corporation Coat-a-Count cortisol kits. HF HRV was assessed using HF power spectral analysis (0.15 to 0.4-Hz). Associations between ED cortisol and HF HRV and 1 month outcomes were assessed via ANOVA and t-tests.
Results: To date, follow-up data has been obtained in 48 of 49 enrolled patients who have reached the 1 month follow-up time point (98%, 28 female, 20 male, age 18-84, mean 36.4 years). ED cortisol and HF HRV levels were associated with 1 month outcome (Tables 1 and 2).
Conclusion: These pilot data suggest that physiologic characteristics of patients assessed in the ED are associated with post-MVC pain and psychological sequelae. These characteristics may assist in the identification of individuals at high risk of pain and psychological sequelae, and may provide new insights into the pathophysiology of these disorders. Updated information from this ongoing trial will be presented at the meeting.

Table 1. Association between mean ED cortisol level and persistent pain and psychological sequelae 1 month after MVC

1 Month Outcome (n)	ED Cortisol (ug/mL)
No Symptoms (26)	.33 ± .46
Pain Only (10)	.27 ± .29

PTSD ± Pain (5)	.18 ± .10
Depression ± Pain (2)	1.48 ± 2.0
Depression & PTSD ± Pain (5)	.52 ± .50
ANOVA F statistic (p value)	2.777 (.039)

Table 2. Association between mean ED HF HRV and presence of early and persistent pain and psychological sequelae

Mean ED HF HRV[1] by Group	**Pain 3-7 days after MVC**	**Moderate or severe neck and/or back pain at 1 Month**	**PTSD at 1 Month**
Present	146±118	185±119	614±661
Not present	566±534	539±583	278±225
t	3.494	2.618	-2.038
p value	.002	.015	.028

[1]High frequency heart rate variability, [2]Defined by Neck pain and back pain summed NRS scores ≥ 10, [3]Defined by IES-R score ≥ 33

Author Disclosure Block: **S.A. McLean**, K12 RR017607-01, 2; **M. Switzer**, None; **C.W. Jones**, None; **M.R. Sochor**, None; **C.R. Newton**, None; **A.D. Withrow**, None; **J. Fowler**, None; **D.A. Williams**, None; **P.K. Stein**, None; **I. Liberzon**, None; **D.J. Clauw**, DAMD 17 00 2 0018, 2; Cypress Biosciences, 5.

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Additional Keyword (Complete):
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Altered Temporal Sequences of Evoked Brain Activity in Fibromyalgia

Author Block: Rupal Patel, Richard H. Gracely, Greta A. Naylor, Brian K. Michalik, Linda M. Skalski, Daniel J. Clauw. Departments of Internal Medicine/Rheumatology, University of Michigan, Ann Arbor, MI

Introduction: fMRI studies of fibromyalgia (FM) have showed augmented pain processing to pressure and heat. This study used brief (5s) painful pressure stimuli and the high temporal resolution of fMRI to assess the sequence of pain-evoked brain activity in healthy controls (HC) and compare this sequence to that observed in FM.
Methods: Twenty female patients (mean age = 45) satisfying ACR criteria for FM and 20 matched HC (mean age = 45) participated in the study. Before fMRI scanning, the effects of painful pressure applied to the left thumbnail were assessed using the Multiple Random Staircase method and a verbal-numerical Box pain scale to determine stimulus pressures sufficient to evoke subjective levels of mild, moderate or intense pain sensations. During 10 min fMRI scans, these pressures were applied to the thumbnail in random sequence during 5s of painful pressure presented at 25 s intervals. fMRI data were acquired by a 3 Tesla scanner every 2.5 s (TR 2.5s, TE 30 ms, FA 90, 64x64 matrix, 48 horizontal slices; spiral acquisition). Analysis of the BOLD signal (head motion correction, slice timing corrections, spatial smoothed 6mm FWHM, intensity normalization, conversion to standard coordinate system, and modeling to an expected haemodymanic response was performed using Medx.
Results: The temporal response was classified as [E]arly, [M]iddle or [L]ate (E = 2.5 sec, M = 5 sec, L = 7.5 sec of haemodynamic lag).

Region	**HC:**	Early	Middle	Late	**FM:**	Early	Middle	Late
Anterior Cingular Cortex (ACC)		*		*				
Cerebellum		*		*			*	*
Thalamus		*	*				*	
Inferior Parietal Lobule (IPL)		*	*				*	
Inferior Frontal Gyrus (IFG)		*	*	*				
Medial Frontal Gyrus (MFG)			*	*			*	
Insula				*				
Basal Ganglia				*			*	
Brainstem				*				
Claustrum							*	

Conclusion: In HC, brief pressure stimuli evoked immediate responses (Thalamus, Cerebellum, ACC, IPL, IFG) and late responses (IFG, MFG, Insula, Brainstem) that were

not observed in FM. This delayed and shortened response in FM contrasts with augmentation observed with longer (25-30s) pressure stimuli, suggesting a tonic inhibitory state that during prolonged stimulation is quickly attenuated, and/or opposed by facilitatory mechanisms.

Author Disclosure Block: **R. Patel**, None; **R.H. Gracely**, Pierre Fabre, 5; **G.A. Naylor**, None; **B.K. Michalik**, None; **L.M. Skalski**, None; **D.J. Clauw**, DAMD 17 00 2 0018, 2; Cypress Biosciences, 5.

Category (Complete): 9. Fibromyalgia and soft tissue disorders
Keywords (Complete): fibromyalgia ; pain ; imaging techniques
Additional Keyword (Complete):
: diffuse noxious inhibitory controls (DNIC)

Eligibility (Complete):
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Stimulation Duration Alters the Initial fMRI Response to Painful Pressure in Fibromyalgia and Healthy Contols

Author Block: Rupal Patel, Brian K. Michalik, Linda M. Skalski, Daniel J. Clauw, Richard H. Gracely. Departments of Internal Medicine/Rheumatology, University of Michigan, Ann Arbor, MI

Introduction: Neuroimaging studies of pain processing usually deliver brief (e.g. 5s) stimuli. fMRI studies of fibromyalgia (FM) have shown augmented pain processing to pressure stimuli of 25-30s duration. To investigate further differences in pain processing in FM, this study compared the initial effects of brief 5s painful pressure stimuli and the first 5s of a 25s stimulus. The analysis evaluated if these identical stimulus conditions are influenced by subsequent stimulus duration during a scanning session in healthy control subjects (HC) and the impact of this effect on pain processing in FM.
Methods: Twenty female patients satisfying ACR criteria for FM and 20 age-matched HC participated in two sessions. Before fMRI scanning, a psychophysical staircase method was used to determine stimulus pressures that evoked slightly intense pain. During 10 min fMRI scans, these pressures were applied to the left thumbnail in random sequence during either 5s of painful pressure presented at 25s intervals or 25s of pressure presented at 50s intervals. fMRI data were acquired by a GE 3 Tesla scanner every 2.5s and analysis of the BOLD signal was performed using Medx (convoluted 5s box car with 2.5s haemodynamic delay). The analysis evaluated the first 5s of stimulation in each condition, which included the entire 5s stimulus and the first 5s of a 25s (5/25s) stimulus.
Results: During equally painful slightly intense stimulation in HC, the 5/25s stimulus evoked unique early activity in bilateral cerebellum (Z= 4.91-5.85), middle frontal gyrus (BA6, 10; Z=3.26-3.73) and ipsilateral hippocampus (Z=3.90). In contrast, the 5s stimulus evoked unique early activity in contralateral thalamic medial dorsal nucleus (MDN, Z=5.16) and bilateral anterior nuclei (Z=3.32-3.60). Additional unique activations were observed in contralateral anterior cingulate cortex (ACC, Z=4.83-5.08), inferior parietal lobule (Z=3.95) and midbrain (Z=4.27). These effects of method were not observed in FM. The 5/25s stimulus evoked unique activations in the contralateral inferior frontal (BA 45, 47; Z=4.13-5.03) and middle frontal (BA 45, 46; Z=3.79-3.80) gyri and in ipsilateral brainstem (Pons, Z=3.81). The 5s stimulus evoked no early activity in FM.
Conclusion: HC response to 5s of stimulation was influenced by the subsequent duration of the stimulus, which may involve somatic mechanisms of sensitization and intrinsic inhibition and psychological mechanisms of anticipation and conditioned responses to stimulation. FM showed a different pattern of responses to the early part of the prolonged stimulus and no effects to the 5s stimulus. This result provided further evidence of altered pain processing in FM and suggests a method that examines temporal patterns rather than magnitude of evoked activity.
Author Disclosure Block: **R. Patel**, None; **B.K. Michalik**, None; **L.M. Skalski**, None; **D.J. Clauw**, DAMD 17 00 2 0018, 2; Cypress Biosciences, 5; **R.H. Gracely**, Pierre Fabre, 5.

Category (Complete): 9. Fibromyalgia and soft tissue disorders
Keywords (Complete): fibromyalgia ; pain ; imaging techniques
Additional Keyword (Complete):
: stimulation duration

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Increased mu-Opioid Receptor Availability is Detected During Clinical Pain Reduction in Fibromylagia Patients

Author Block: David J. Scott[1], Richard E. Harris[2], Greta A. Naylor[2], John B. Romond[2], Adrielle R. Bradford[2], Richard H. Gracely[2], Daniel J. Clauw[2], Jon-Kar Zubieta[3]. [1]Molecular and Behavioral Neuroscience Institute, University of Michigan, Ann Arbor, MI; [2]Departments of Internal Medicine/Rheumatology, University of Michigan, Ann Arbor, MI; [3]Psychiatry, Radiology, and Mental Health Research Institute, University of Michigan, Ann Arbor, MI

Purpose: Fibromyalgia involves chronic, widespread idiopathic pain, yet the biological mechanisms underlying this disease remain poorly understood. As endogenous opioids play a key role in modulating pain perception, we investigated the role of mu-opioid receptor (MOR) activity in fibromyalgia patients.
Methods: 11 female patients diagnosed with fibromyalgia were examined using positron emission tomography (PET) and [^{11}C]carfentanil, a MOR selective radiotracer. Patients met ACR 1990 criteria for the diagnosis of fibromyalgia for at least 1 year. During the scanning session patients underwent one acupuncture or one sham acupuncture intervention. For the purpose of this analysis, data from both groups were combined. Pain report was recorded immediately before and after the intervention using GBSintensity, GBSunpleasantness, and a Visual Analog Scale (VAS). Logan plots were created to obtain maps of whole-brain MOR binding potential (BP) at baseline and following the intervention. Changes in opioid binding between conditions were assessed using SPM99, and regions showing significant differences in BP were extracted using locally developed software. Correlations between pain report and MOR occupancy were performed in SPSS.
Results: Following the intervention, patients reported significantly reduced clinical pain as measured by all three scales (GBSintensity: $p = .001$; GBSunpleasantness: $p = .02$; VAS rating: $p < 0.02$). Patients also showed significantly increased ($p < 0.0005$) MOR availability in the left nucleus accumbens ($z = 9.0$) and amygdala bilaterally (left, $z = 10.1$; right, $z = 9.8$) following the intervention. The percent increase in MOR occupancy within the nucleus accumbens was significantly correlated with reductions in all clinical measures (GBSintensity: $r = 0.60$, $p = 0.05$; GBSunpleasantness: $r = 0.84$, $p = 0.001$; VAS: $r = 0.73$, $p = 0.01$).
Conclusions: We report that increased MOR availability is associated with improved pain report in fibromyalgia patients. These results implicate short-term modulation of this analgesic system in chronic pain reduction. As such, the endogenous opioid system may play a role in future trials investigating fibromyalgia.
Author Disclosure Block: **D.J. Scott**, None; **R.E. Harris**, None; **G.A. Naylor**, None; **J.B. Romond**, None; **A.R. Bradford**, None; **R.H. Gracely**, Pierre Fabre, 5; **D.J. Clauw**, DAMD 17 00 2 0018, 2; Cypress Biosciences, 5; **J. Zubieta**, None.

Category (Complete): 9. Fibromyalgia and soft tissue disorders
Keywords (Complete): fibromyalgia ; opioids ; pain
Additional Keyword (Complete):
: PET, acupuncture

Eligibility (Complete):
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Activity: ACR Abstract Submission
Current Date/Time: 5/8/2006 10:22:41 AM

Pre-MVC Symptom and Psychological Characteristics are Associated with Persistent Pain and Psychological Symptoms after MVC

Author Block: Michael Switzer[1], Samuel A. McLean[1], Christopher W. Jones[1], Mark R. Sochor[1], Christopher R. H. Newton[2], Amanda D. Withrow[1], Jennifer Fowler[2], David A. Williams[3], Israel Liberzon[4], Daniel J. Clauw[3]. [1]Emergency Medicine, University of Michigan, Ann Arbor, MI; [2]Emergency Medicine, St. Joseph Mercy Hospital, Ypsilanti, MI; [3]Departments of Internal Medicine/Rheumatology, University of Michigan, Ann Arbor, MI; [4]Psychiatry, University of Michigan, Ann Arbor, MI

Purpose: Chronic musculoskeletal pain and psychological sequelae are common after motor vehicle collision (MVC), but the etiology of these disorders are not well understood. Somatic symptoms and psychological factors are identified risk factors for chronic pain and psychological disorder development in other settings, but the relative influence of these factors on post-MVC outcomes has not previously been examined.

Material and Methods: Patients being evaluated in the emergency department (ED) after MVC were recruited into an ongoing multicenter study which includes ED baseline assessment and 1-month outcome evaluation. ED evaluation included an assessment of somatic symptoms, depressive symptoms (CES-D), anxiety symptoms (STPI), and perceived stress (Cohen) in the calendar month prior to the MVC. One-month outcome assessment includes evaluation of persistent MVC-related neck or back pain symptoms, PTSD symptoms (IES-R), and depressive symptoms (CES-D). Associations between baseline psychological and somatic symptoms and 1-month outcomes were assessed via correlation analyses.
Results: To date, follow-up data has been obtained in 48 of 49 enrolled patients who have reached the 1-month follow-up time point (98%, 28 female, 20 male, age 18-84, mean 36.4 years). Comparison of baseline symptom and psychological factors and 1-month outcomes are shown in Table 1. Baseline somatic symptoms were strong predictors of both 1-month pain and psychological sequelae of MVC. Baseline anxiety and depressive symptoms and perceived stress were strong predictors of psychological outcomes but not pain outcomes.
Conclusion: These pilot data suggest that somatic symptoms are strong predictors of MVC-related pain and psychological sequelae. Baseline psychological factors appear to be strong predictors of psychological sequelae but may be less predictive of chronic MVC-related pain. Updated information from this ongoing trial will be presented at the meeting.

Table 1. Association between pre-MVC psychological symptoms and early and persistent pain and psychological sequelae 1 month after MVC

Pre-MVC psychological	Mood Outcomes	PTSD Outcomes	Pain Outcomes

factor	Mood Interference 3-7 days after MVC	Depressive Symptoms 1 month after MVC	PTSD Symptoms[1] 1 Month after MVC	Pain Symptoms[2] 1 Month after MVC
Somatic[3] symptoms	.350 (.025)	.519 (.000)	.444 (.002)	.363 (.014)
Anxiety[4] Symptoms	.278 (.079)	.469 (.002)	.418 (.005)	-.061 (694)
Perceived[5] Stress	.119 (.448)	.266(.085)	.072 (.636)	-128 (.395)
Depressive[6] Symptoms	.126 (.457)	.461 (.004)	.268 (.103)	-.100 (.546)
[1]IES-R, [2]Sum of MVC-related neck or back pain (0-20 NRS), [3]Symptoms listed in text, [4]STPI, [5]Cohen Perceived Stress Scale, [6]CES-D				

Author Disclosure Block: **M. Switzer**, None; **S.A. McLean**, K12 RR017607-01, 2; **C.W. Jones**, None; **M.R. Sochor**, None; **C.R. Newton**, None; **A.D. Withrow**, None; **J. Fowler**, None; **D.A. Williams**, None; **I. Liberzon**, None; **D.J. Clauw**, DAMD 17 00 2 0018, 2; Cypress Biosciences, 5.

Category (Complete): 9. Fibromyalgia and soft tissue disorders
Keywords (Complete): pain ; musculoskeletal disorders ; trauma
Additional Keyword (Complete):
: posttraumatic stress disorder (PTSD)

Eligibility (Complete):
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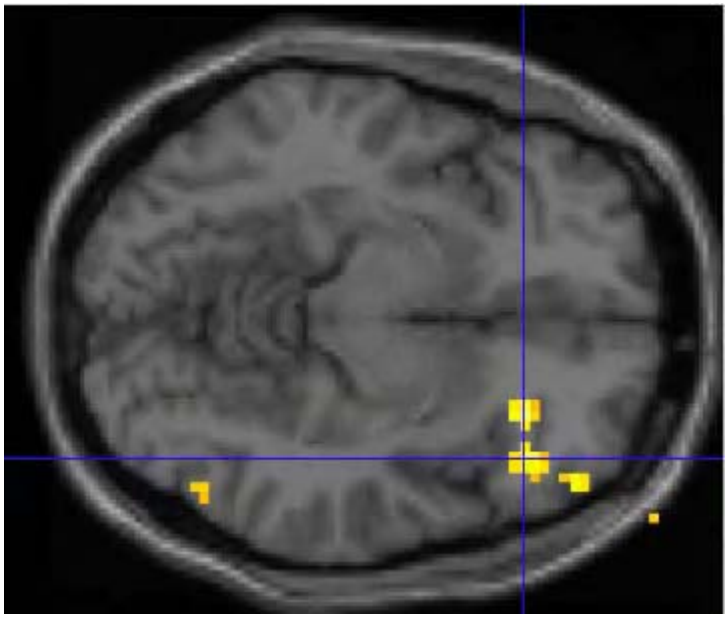
Activity: ACR Abstract Submission
Current Date/Time: 5/8/2006 2:43:33 PM

Altered Pain Functional Connectivity (fcMRI) at Rest in Fibromyalgia

Author Block: Robert C. Welsh[1], Sumati Krishnan[2], Rupal Patel[3], Daniel J. Clauw[3], Richard H. Gracely[3]. [1]Department of Radiology/University of Michigan, Ann Arbor, MI; [2]Department of Biomedical Engineering/University of Michigan, Ann Arbor, MI; [3]Department of Internal Medicine/Rheumatology, University of Michigan, Ann Arbor, MI

Introduction: During rest (no stimulation) the brain assumes a pattern of activity that can be detected by low-frequency oscillations of the BOLD signal. This approach is termed functional connectivity MRI (fcMRI). This study investigates the hypothesis that the pain network in fibromyalgia patients, which has been shown to be altered during painful stimulation, is also altered during rest.
Methods: Ten fibromyalgia patients aged 31-57 years and ten healthy controls aged 23-58 years were scanned on a 3T MRI. Subjects laid quietly, with eyes open, in an MRI scanner viewing a fixation cross during a 6-minute data acquisition session. Whole-brain T2* weighted images were acquired every 2.5 seconds. Recordings of respiration and cardiac cycle were made by a respiratory belt and pulse oximeter. Time-series data were corrected for physiological variance, slice-time corrected and band-pass filtered (0.01-0.10 Hz). Regions of interest in the posterior cingulate cortex (PCC) were drawn for each subject. Cross-correlation was made between the voxel-averaged time-course in the PCC with all other voxels in the brain. Correlation maps were transformed into Z-maps and warped to a standard space (MNI). Paired t-tests were performed to verify patterns of activity in each group. Group differences in activation were assessed by an unpaired t-test.
Results: Both groups showed typical resting patterns of activation. Comparison between groups showed increased connectivity in a region near the insula/orbital cortex in fibromyalgia patients. The figure shows two clusters of increased activity (extent = 15 voxels; Z = 3.60; extent 28 voxels, Z = 3.49).
Conclusion: In comparison to controls, fibromyalgia patients show increased functional interconnections within the pain network during rest.



Author Disclosure Block: **R.C. Welsh**, None; **S. Krishnan**, None; **R. Patel**, None; **D.J. Clauw**, DAMD 17 00 2 0018, 2; Cypress Biosciences, 5; **R.H. Gracely**, Pierre Fabre, 5.

Category (Complete): 9. Fibromyalgia and soft tissue disorders
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Additional Keyword (Complete):
Eligibility (Complete):
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Activity: ACR Abstract Submission
Current Date/Time: 5/8/2006 10:16:22 AM

Cognitive and Behavioral Factors Assessed 3-7 Days after Motor Vehicle Collision are Associated with Persistent Pain and Psychological Symptoms

Author Block: Amanda D. Withrow[1], Samuel A. McLean[1], Mark R. Sochor[1], Christopher R. H. Newton[1], Michael Switzer[1], Jennifer Fowler[2], Daniel J. Clauw[3], David A. Williams[3]. [1]Emergency Medicine, University of Michigan, Ann Arbor, MI; [2]Emergency Medicine, St. Joseph Mercy Hospital, Ypsilanti, MI; [3]Departments of Internal Medicine/Rheumatology, University of Michigan, Ann Arbor, MI

Purpose: Chronic musculoskeletal pain and psychological sequelae are common after MVC, but the etiology of these disorders are not well understood. Cognitive and behavioral factors following MVC are suspected to contribute to the development of persistent pain and psychological symptoms, but the influence of these factors, assessed in the early posttraumatic period, has not previously been examined.
Material and Methods: Patients being evaluated in the emergency department (ED) after MVC were recruited into an ongoing multicenter study which includes ED baseline assessment, 3-7 day post-MVC assessment, and 1 month outcome evaluation. 3-7 day assessment includes brief versions of pain beliefs and coping strategies measures (i.e. SOPA; PBAPI; CSQ) and a brief assessment of social support (MSSS). One month outcome assessment includes evaluation of persistent MVC-related neck pain or back pain symptoms (each rated on a 0-10 numeric rating scale) and PTSD symptoms (IES-R). Associations between pain beliefs and coping strategies, social support and 1 month outcomes were assessed via correlation analyses.
Results: To date, follow-up data has been obtained in 48 of 49 enrolled patients who have reached the 1 month follow-up time point (98%, 28 female, 20 male, age 18-84, mean 36.4 years). Comparison of cognitive behavioral factors and 1 month outcomes are shown in table 1. Pain coping methods were strongly associated with both 1 month pain and psychological sequelae of MVC. Associations with 1 month pain outcomes persisted after adjusting for the severity of initial pain symptoms. There was no relationship between social support and 1 month pain or PTSD symptom outcomes.
Conclusion: These pilot data suggest that pain beliefs and coping strategies are predictive of pain and psychological sequelae after MVC. Updated information from this ongoing trial will be presented at the meeting.

Measure (Assessed 3-7 days after MVC[1])	**Neck and Back Pain Severity 1 Month after MVC**		**Correlation with PTSD[3] Symptoms 1 month after MVC assessed via IES-R[4]**
Survey of Pain Attitudes Items[5]	**Unadjusted r value (p value)**	**Adjusted for initial pain severity[2]**	
Pain Control	-.317 (.038)	-.285 (.074)	-.471 (.002)
Disability	.453 (.002)	.464 (.003)	.409 (.007)

Harm	.146 (.350)	.100 (.541)	.217 (.167)
Emotion	.429 (.004)	.406 (.009)	.552 (.000)
Medication	.572 (.000)	.571 (.000)	.473 (.002)
Solicitude	.339 (.026)	.302 (.058)	.206 (.190)
Medical cures	-.494 (.001)	-.473 (.002)	-.258 (.099)
Pain Beliefs and Perceptions Inventory Items[5]	**Unadjusted**	**Adjusted for initial pain severity**	**PTSD Symptoms 1 month after MVC**
Mystery	.226 (.144)	.195 (.228)	.527 (.000)
Acceptance	.426 (.004)	.421 (.007)	.415 (.006)
Constancy	.511 (.000)	.467 (.002)	.451 (.003)
Self-Blame	-.239 (.123)	-.205 (.205)	-.226 (.151)
Coping Strategies Questionnaire Items[5]	**Unadjusted**	**Adjusted for initial pain severity**	**PTSD Symptoms 1 month after MVC**
Diverting attention	.042 (.788)	.103 (.528)	.014 (.930)
Reinterpreting pain sensation	-.089 (.569)	-.061 (.710)	.114 (.473)
Catastrophizing	.394 (.009)	.340 (.032)	.461 (.002)
Ignoring sensations	-.329 (.031)	-.284 (.075)	-.502 (.001)
Praying / Hoping	.274 (.076)	.227 (.158)	.216 (.168)
Coping self statements	-.101 (.521)	-.042 (.797)	-.090 (.572)
Increased behavioral activities	-.237 (.126)	.187 (.247)	-.302 (.052)

[1]Motor vehicle collision, [2]Global pain severity assessed in the emergency department using a 0-10 numeric rating scale, [3]Posttraumatic stress disorder, [4]Impact of Event Scale-Revised, [5]Brief version (Jensen et al 2003)

Author Disclosure Block: **A.D. Withrow**, None; **S.A. McLean**, K12 RR017607-01, 2; **M.R. Sochor**, None; **C.R. Newton**, None; **M. Switzer**, None; **J. Fowler**, None; **D.J. Clauw**, DAMD 17 00 2 0018, 2; Cypress Biosciences, 5; **D.A. Williams**, DAMD 17 00 2 0018, 2.

Category (Complete): 9. Fibromyalgia and soft tissue disorders
Keywords (Complete): pain ; musculoskeletal disorders ; trauma
Additional Keyword (Complete):
: posttraumatic stress disorder (PTSD)

Eligibility (Complete):

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“Living Well with Fibromyalgia”

Website Screen Shots

Study Title: Internet and Telehealth Enhanced CBT for the Management of Fibromyalgia

Partnership with Avera-McKennan Research Hospital, Sioux Falls, SD

LIVING WELL with Fibromyalgia

developed by the Avera Research Institute and the University of Michigan

LIVING WELL with Fibromyalgia

developed by the Avera Research Institute and the University of Michigan

goal buddy
educational CD
monthly assessment
community message board

Having technical difficulties? Please contact Kevin Smith averaresearch@mckennan.org

goal buddy

Tue. Sep. 19, Week 38, 2006

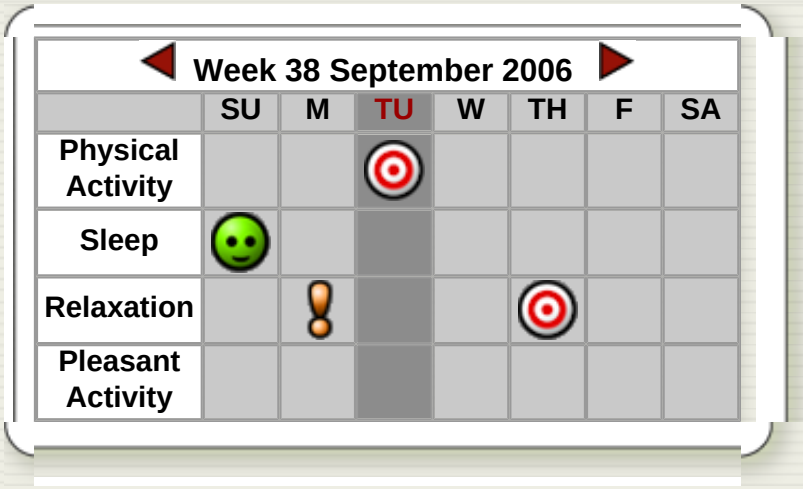
Welcome Michael,

You have met 1 of your 4 goal(s) so far this week.

You have 1 goal (s) planned today and 1 goal(s) for later this week.

To schedule goals, click on a day and a specific lifestyle behavior.

To evaluate past goals, click on the orange exclamation point.



Key

- Goal is planned.
- Goal was planned; due for evaluation.
- Achieved goal.
- Did not achieve goal; would like help using the problem solving cycle.
- Did not do it, and I don't want help.

For help using the Living Well with Fibromyalgia tools, please contact Susan Weaver averaresearch@mckennan.org